DISSERTATION TITLED

"PREDICTION OF ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS BY USING FIBROSCAN, SPLEEN SIZE AND PLATELET COUNT"

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CERTIFICATE

This is to certify that the dissertation entitled **"PREDICTION OF ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS BY USING FIBROSCAN, SPLEEN SIZE AND PLATELET COUNT"** is a bonafide work done by **DR. M.PRASANNAKUMAR**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, during march 2014 to august 2014 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2012 - 2015.

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DECLARATION

I solemnly declare that the dissertation entitled **"PREDICTION OF ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS BY USING FIBROSCAN, SPLEEN SIZE AND PLATELET COUNT"**is done by me at Madras Medical College, Chennai-3 under the guidance and supervision of Prof. S.TITO, M.D., to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I.

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(DR.M.Prasannakumar)

LISTS OF ABBREVIATIONS

CLD	:	Chronic Liver Disease
EV	:	Esophageal Varices
EVL	:	Endoscopic Variceal Ligation
GI	:	Gastro Intestinal
HBV	:	Hepatitis B Virus
HCC	:	Hepatocellular Carcinoma
HCV	:	Hepatitis C Virus
HREV	:	High Risk Esophageal Varices
HVPG	:	Hepatic Venous Pressure Gradient
INR	:	International Normalised Ratio
LEV	:	Large Esophageal Varices
LS	:	Liver Stiffness
MELD	:	Model For End Stage Liver Disease
MCV	:	Mean Corpuscular Volume
MCHC Concentration	:	Mean Corpuscular Hemoglobin
MRA	:	Magnetic Resonance Angiography
NO	:	Nitric Oxide
NSAIDS	:	Non Steroidal Anti Inflammatory Agents

OGD	:	Esophagogastro Duodenoscopy
PCV	:	Packed Cell Volume
PC/SD RATIO	:	Platelet Count To Spleen Diameter Ratio
PHT	:	Portal Hypertension
PLT	:	Platelet Count
RBC	:	Red Blood Cells
SAAG	:	Serum Ascites Albumin Gradient
SD	:	Standard Deviation
SGOT Transaminase	:	Serum Glutamate Oxaloacetate
SGPT	:	Serum Glutamate Pyruvate Transaminase
TIPS Shunt	:	Transjugular Intrahepatic Portosystemic
US	:	Ultrasonography
WHVP	:	Wedged Hepatic Venous Pressure Gradient

CONTENT

ABSTRACT

Background and objectives:

Patients with cirrhosis of liver according to current guidelines and recommendation need to undergo screening with an OGD scopy to detect esophageal varices and to institute prophylactic measures in patients with large esophageal varices at the time of diagnosis and during follow up. This poses social and medical burden due to the greater number of cirrhotic patients and lesser number of endoscopy units. In this study we aim to identify the non invasive predictors of esophageal varices particularly fibroscan, spleen size, platelet count and platelet count/ spleen diameter ratio.

Methods

In this observational study of 50 patients, newly diagnosed patients with chronic liver disease without a history of gastro intestinal bleeding were included between march 2014 and September 2014. Relevant clinical parameters were assessed which included physical examination, complete hemogram, biochemical work up, liver stiffness measurement using fibroscan , USG measurement of spleen long axis diameter, OGD scopy . platelet count/ spleen diameter ratio was calculated for all patients.

Results

Among the 50 patients studied males predominated the study with 86%. Out of the study population 88% of the patients had varices. For a cut off point of fibroscan value > 32 ,the sensitivity was 79.5% and specificity was 100% . A statistically significant correlation between fibroscan values and presence of varices was noted (P ==0.001). for a cut off value of platelet count/ spleen diameter the sensitivity was 68.2% and statistical correlation was sgnifican(P = for the prediction of varices.

CONCLUSION:

From our study we conclude that fibroscan is a valuable tool in the prediction of presence of esophageal varices. But the cut off values differ from study to study which needs to be validated. A lower PC/SD ratio determine the presence of highgrades of varices. From all these parameters we could identify the subset of patients who require OGD scopy for the prophylactic management of esophageal varices. Therefore avoiding unnecessary endoscopy screenings and reducing the burden of endoscopy units. Apart from being non invasive these parameters are easily reproducible.

Key words : Fibroscan, esophageal varices, chronic liver disease, platelet count to spleen diameter ratio, thrombocytopenia

INTRODUCTION

Chronic liver disease is characterized by gradual destruction of hepatic tissue over time. The most common and deadly complication of chronic liver diseases is portal hypertension. Gastro esophageal varices, ascites, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome and hypersplenism develop as a consequence.

The term portal hypertension was coined by Gilbert in 1902. However it was not until that Thompson could verify the increase in portal pressure directly during laparotomy that portal hypertension was confirmed. It was way back in 1650 that Glisson at a dissection in London, established the portal vein as the vessel by which blood was collected from the gastrointestinal tract and returned to the systemic circulation. As early as 1543, Vlius drew an anatomical picture of the portal venous system.[2] Variceal hemorrhage is a life threatening complication with 20-30% mortality rate being associated with every episode of bleeding[2.]

The grade of esophageal varices often correlates with the severity of the liver disease. Around 40% of decompensated cirrhosis patients have varices during the time of diagnosis. 8% per year is the rate of

formation of varices and it develop during long term follow up in many patients.

About 50% of cirrhotic patients develop gastroesophageal varices. 5-33% of patients with portal hypertension develop gastric varices. The frequency of esophageal varices is 30-70% in cirrhotic patients and 9-36% of patients present with “high-risk” varices. 4-30% of cirrhotic patients presenting with small varices would develop large varices every year and will be at risk of bleeding.

Approximately 30% of patients with cirrhosis present with esophageal varices at the time of diagnosis, reaching 90% after 10 years. At 6 weeks the mortality rate of 20%is found due to bleeding from esophageal varices. Variceal bleeding is the most common fatal complication in cirrhotic patients.[5]

The severity of liver cirrhosis can be assessed using CHILD – PUGH score. Within the first year about 30% of patients with esophageal varices would bleed after diagnosis. The severity of the underlying disease will determine the mortality due to bleeding episodes.

In such bleeding episode the resulting mortality may vary from <10% in compensated cirrhosis with child pugh score of A to >70% in those patients with child pugh C advanced stage of cirrhosis. The risk of

re-bleeding is 80% within one year. Within 1-2 years after the index hemorrhage about 60% of patients who are not treated will develop “late – re-bleeding”.

Around 1/3rd would re-bleed within 6 weeks of initial episode. Among these episodes 40% will take place within 5 days of initial episode of bleeding.

Over the last decades clinical trials and research on animal models have evolved and led to current recommendations for management. Baveno V conference and AASLD GUIDELINES are considered for practical approach for management. Current recommendation suggest that every patient who is newly diagnosed of cirrhosis should have an esophagogastroduodenoscopy to look for the presence of varices and also the size of varices. Surveillance endoscopies are advised based on the size and presence of varices and the level of cirrhosis.

For patients with compensated cirrhosis and NO varices –repeat endoscopy is recommended every 2-3 years. For patients with small varices OGD is repeated every 1-2 years.

For patients with decompensated cirrhosis endoscopy is done at yearly intervals.

However this approach has 2 disadvantages [8]. Endoscopy is a tool which is invasive and cost effectiveness of OGD scopy is quite questionable since 9-36% of patients with chronic liver disease are observed to have varices on OGD scopy . It may be better cost effective if only high risk beneficiaries undergo routine screening for the presence of varices hence as reducing the inconvenience of patients and also OGD scopy units . there are factors that predict risk for initial episode of variceal hemorrhage. A lot of clinical, laboratory and USG parameters are there when either as a single or in combination have good predictive power for non invasive assessment of risk of bleeding from varices. However these factors which predict the presence of varices are not defined clearly.

Acknowledgement of non invasive predicting tools of esophageal varices will be helpful for eveyone to perform OGD scopy in particular group of patients thus avoiding unwanted invasive procedures and expenditure, at the same time high risk patients are not missed with increased chances of hemorrhage.

Currently many non invasive methods have been used to predict the presence of esophageal varices. Overall ,the most common result of these studies show that large spleen size, low platelet count, or their combination (platelet count to spleen diameter ratio),fibroscan ,portal

vein size or presence of collaterals on ultrasound, hypersplenism and child pugh score were the predictors of esophageal varices either directly or indirectly linked to portal hypertension.[9]

In a study by Thomopoulus et al (2003) seventten variables considered relevant to the presence of esophageal varices were tested and came to conclusion that thrombocytopenia, splenomegaly and ascites are independent predicting tools of large esophageal varices in cirrhotic patients. The author gives suggestion that endoscopy could be avoided safely in cirrhotic patients with none of these predictive factors, as large varices are absent in this group of patients.

Anyhow , in patients having a chronic liver disease the presence of Reduction in counts of platelets may depend on many factors other than portal hypertension ,like the mean lifetime of the platelets may get reduced, synthesis of thrombopoietin may be reduced, or marrow suppressive effects of ethanol or hepatitis viruses. On the other side, the evidence of enlargement of spleen in patients with chronic liver diseases is ultimately the impact of changes in the blood vessels that are usually linked to portal hypertension. Having such idea in mind, in the view of Gianni et al(2003),their study applied the platelet count /spleen diameter ratio to be a factor associating reduction in platelet counts to

spleen size in an idea of introducing a factor that takes into account of the thrombocytopenia ,which is most likely depends on hypersplenism.

According to Gianni et al (2003) by applying the platelet count/ spleen Size ratio might have put an end for performing unwanted OGD scopy in every patients having a cut off of > 909 not having the risk of going undiagnosed of esophageal varices.

More recently transient elstography (fibroscan) which estimates liver stiffness (LS) , has been a new method to diagnose esophageal varices with cirrhosis non invasively. While the accuracy of fibroscan in predicting clinically significant portal hypertension is good, its discriminative ability of predicting varices needs further validation.

The combination of different methods may overcome the accuracy of single test by considering various pathophysiological components of portal hypertension. Recent study shows, the combination of 3 simple methods _ fibroscan, spleen size and platelet count proved to be of high accuracy in diagnosing and to rule out varices in patients with compensated hepatitis B virus related chronic liver disease. However data from Indian studies on fibroscan for prediction of esophageal varices not much available.

Our study is aimed at the prediction of esophageal varices by using non invasive tools like fibroscan, spleen size and platelet count.

AIMS AND OBJECTIVES

1. To study on the prediction of esophageal varices in chronic liver disease patients using fibroscan, spleen size and platelet count.

2. To compare these non invasive markers with upper gastro intestinal endoscopy for the presence of varices.

REVIEW OF LITERATURE

CIRRHOSIS denotes a late stage of progressive liver fibrosis characterized by the development of regenerative nodules and distortion of liver architecture.[3] It is usually an irreversible process in the late stages at that point liver transplantation becomes the only left over option. Nonetheless in the earlier stages, cirrhosis is found to be a reversible process in various forms of hepatic disease.[4]

Evolution of cirrhosis [10]

The typical pathological features is a reflection of a chronic insult which cannot be reversed, to the hepatic parenchyma, which is inclusive of widespread fibrosis along with formation of regenerative nodules. These features result from liver cell necrosis, collapse of anchoring reticulin network with subsequent piling up of connective tissue , destruction of vascular bed, and nodular regeneration of left over liver parenchyma. The pathological process should be considered as a ultimate common pathway of many types of long standing liver injury. Clinical features of cirrhosis derived from changes in the morphology and frequently a reflection of the severity of liver damage rather than the causative factor of the existing liver disease. Lack of functioning liver cell tissue may result in jaundice, edema, bleeding diathesis, and a

variety of metabolic alterations; fibrosis and collapsed vasculature lead to portal hypertension and its consequences, including gastro esophageal varices and enlargement of spleen. Ascites and hepatic encephalopathy result from both liver cell insufficiency and portal hypertension.

Classification of cirrhosis[12]

Three anatomical types of cirrhosis

- Micronodular
- Macronodular
- Mixed

Micronodular cirrhosis has characteristic feature of thick regular septae, regenerating tiny nodules with subtle change in size and by involving each lobule.

Macronodular cirrhosis represented by impaired capacity for regrowth as in ethanol intake, malnutrition, older age or anaemia.

Regenerative changes in a micronodular cirrhosis results in macronodular or mixed architecture. In due course of time micronodular cirrhosis often gets converted into macronodular.

Etiology

- Alcohol
- Viral hepatitis types B ± delta, type C
- Metabolic, eg; hemochromatosis, Wilsons, α1 antitrypsin deficiency, cystic fibrosis
- Autoimmune hepatitis
- NASH
- Biliary cirrhosis :primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune cholangiopathy
- Cardiac cirrhosis
- Cryptogenic cirrhosis
- Indian childhood cirrhosis

Diagnosis of cirrhosis

a) **Clinical history:** History of fatigue, easy bruising, pedal edema, fever, abdominal distension, abdominal pain, hemetemesis, malena, high coloured urine, jaundice, weight loss, pruritus, altered sleep pattern or confusion. Risk factors for chronic liver disease like history of hepatitis, alcohol consumption, diabetes mellitus, drug intake, transfusion, family history of hepatic disorders and autoimmune disorders.

b) **Examination:** spider angioma, palmar eryhema, dupytrens contracture, gynecomastia, testicular atrophy, ascites, capud medusa, nail changes; muehrcke's nails, terry nails, hepatomegaly, splenomegaly, icterus, fetor hepaticus, parotid

enlargement neurological changes: mental function , stupor, asterixis.

c) **Investigations :** aminotransferase; aspartate and alanine, their ratio, alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, albumin, prothrombin time, INR ,serum sodium, hematological abnormalities; anaemia, thrombocytopenia, leucopenia and neutropenia, serum immunological tests: hepatitis B antigen, anti HCV , alpha fetoprotein, smooth muscle antibodies, mitochondrial antibodies

USG

By the use of USG ,cirrhosis is predicted by nodules on the surface of liver and portal vein mean flow velocity. The caudate lobe becomes enlarged when compared to the right lobe. Regenerative nodules can be visualized as localised lesions.

Computed tomography

Computed tomography is economical for diagnosing of cirrhotic patients and its complication. Any enlargement of the liver tissue can be measured and the irregular nodules on the surface is visualised. After I.V. contrast , the portal vein can be visualized in the liver, and a collateral circulation with increase in size of spleen may give confirmation to the diagnosis of portal hypertension. Ascites can be identified.

Liver Biopsy

It may be helpful to confirm the diagnosis. It is usually withheld in patients with alcoholic hepatitis and those who continue to consume alcohol until abstinence has been maintained for a minimum period of six months to determine the residual, non reversible disease. Sensitivity is around 80-100% and it depends upon the method used, and the size and number of specimens obtained. If the clinical, radiological and lab data is strongly suggestive of cirrhosis liver biopsy may not be needed. Eg; patient with ascites, nodular shrunken liver on ultrasound abdomen and with severe coagulopathy. Reticulin and collagen stains are essential for the demonstration of a rim of fibrosis around the nodule.

EEG : it may be indicated if neuropsychiatric manifestations are present and to detect early changes in pre-coma.

LIVER STIFFNESS MEASUREMENT

A sonographic technique for assessing liver stiffness has been developed. Initial assessment suggest that it has good test characteristics in advanced fibrosis patients.

MRI – its role in the diagnosis of cirrhosis remains unclear.

NUCLEAR STUDIES: Radionucleotide studies are found useful in the diagnosis of cirrhosis.

STAGING OF CIRRHOSIS [12] Recently a revised staging of cirrhosis classified cirrhosis as compensated and decompensated.

Decompensated cirrhosis is defined by the presence of complications secondary to portal hypertension: ascites, variceal bleeding and/or hepatic encephalopathy.

Clinically patient may have fatigue, muscle wasting and weight loss. Gram negative bacteremia may produce mild fever which is often continuous. Other reasons for fever may be ongoing liver cell necrosis, continuing alcoholic hepatitis or complicating HCC.

Asterixis may be present. Presence of jaundice denotes that hepatic cell destruction is exceeding the regenerative capacity and is viewed seriously. Intensity of jaundice is directly proportional to hepatic cell dysfunction. Other features are pigmentation of skin, purpuric spots over arms, shoulder and tibial shin and is an indicator of low platelet count, clubbing, spider angiomata, white nails, testicular atrophy, hepatomegaly, splenomegaly.

Compensated cirrhosis[11] is composed of two sub stages- without varices or with varices. In compensated patients without varices the development of varices and decompensation is predicted by the degree of portal hypertension. So compensated cirrhosis is further divided into

patients with clinically significant portal hypertension and without portal hypertension or portal hypertension which is not clinically significant. The diagnosis of decompensated cirrhosis is done clinically whereas sub staging of compensated cirrhosis needs OGD scopy for diagnosing varices and HVPG measurement for estimation of portal pressure.

Markers of cirrhosis are spider angiomata, palmar erythema , pedal edema, unexplained epistaxis, hepatomegaly, splenomegaly. Such patients remain in compensated stage until their death due to other cause. Precipitating factors for decompensation are bacterial infection, toxins, trauma or surgery.

ASSESSMENT OF SEVERITY AND PROGNOSIS

Severity may be measured by

1. Child pugh scoring system
2. MELD scoring system
3. Liver biopsy

Cirrhosis can be staged clinically. A reliable staging system is the modified child pugh classification with a scoring system of 5-15. This system was stipulated for risk stratification of patients before undergoing portal decompressive operation.

CHILD PUGH CLASSIFICATION [10,]

Child pugh classification			
	A **1 point**	**B** **2 points**	**C** **3 points**
s. bilirubin	<2	2-3	>3
s. albumin	>3.5	2.8-3.5	<2.8
Ascites	None	Easily controlled	Poorly controlled
Prothrombin time(raise) INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Minimal	Coma

Child pugh score interpretation

5-6 points: child score A
7-9 points: child score B
10-15 points: child score C

The child pugh score is a reasonably reliable predictor of survival in most of the hepatic disease and predicts the possibility of major complications of liver cirrhosis like variceal bleeding and spontaneous bacterial peritonitis. It has been used to assess the prognosis in cirrhosis and to provide the standard criteria for listing transplantation of liver.

MELD SCORE [13,17]

Recently the child pugh classification system has been replaced by MELD SCORE for assessing the necessity of liver transplantation. Model for end stage liver disease score is a prospective scoring system used for predicting the prognosis of hepatic disease and portal hypertensive patients. It is calculated by the use of 3 non invasive variables – serum creatinine, the prothrombin time expressed as INR and serum bilirubin model for end stage liver disease provide a more objective aspect to assess severity of the disease and has less variation with centre to centre than child pugh classification and the range of values are wider. Pediatric end stage liver system is a similar type of scoring system adopted for children <12 years.

MELD =3.8[Ln serum bilirubin(mg/dl)] + 11.2[Ln INR] + 9.6[Ln serum creatinine(mg/dl)] + 6.4

SCORE	THREE MONTH MORTALITY RATE(%)
>40	71.3
30-39	52.6
20-29	19.6
10-19	6
<9	5

Other clinical settings MELD score used are for predicting mortality in : alcoholic hepatitis, hepatorenal syndrome, fulminant hepatic failure, sepsis in cirrhosis, acute variceal bleeding, surgical procedure in CLD patients and TIPS procedure.

PORTAL HYPERTENSION[10-13]

Portal hypertension is defined as the elevation of hepatic venous pressure gradient (HVPG) to > 5mm Hg.

Clinically significant Portal hypertension : when portal pressure gradient increases above the threshold value of 10 mmHg or 12 mmHg ,portal hypertension is known to be clinically significant. Portal pressure gradient values between six and ten mmHg known as subclinical portal hypertension.

Portal pressure gradient is calculated by the product of vascular resistance inside the portal venous system and blood flow.

Portal pressure is calculated clinically by hepatic venous pressure gradient(HVPG) measurement.

HVPG is the difference between wedged hepatic venous pressure and free hepatic venous pressure.

HVPG exactly reflect the portal pressure in viral cirrhosis and alcoholic cirrhosis.

ANATOMY

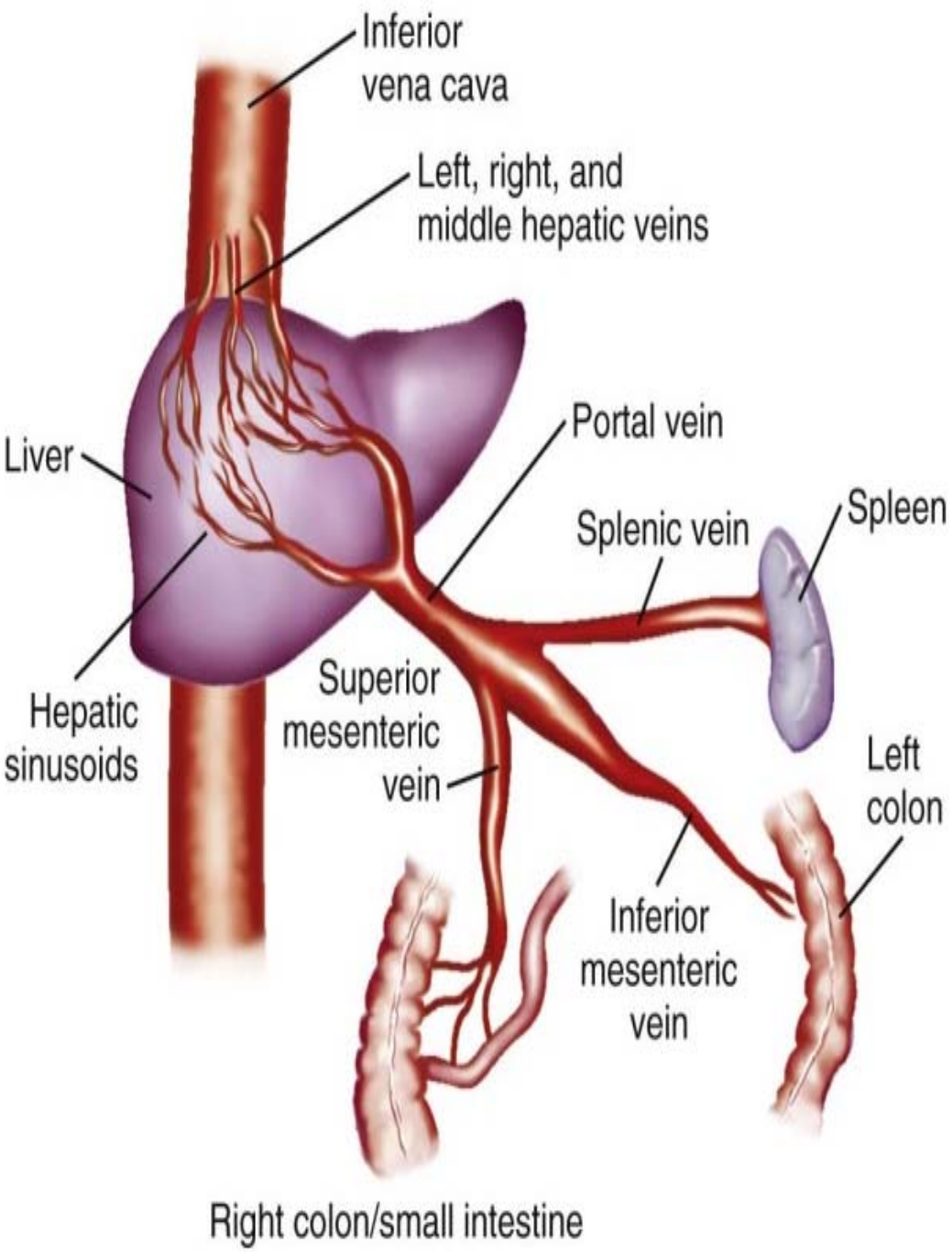
The confluence of splenic vein and superior mesenteric vein forms the portal vein , behind the neck of pancreas. The length of portal vein is about 7.5 cm . it runs into the hilum of liver, posterior to the bile duct and hepatic artery. The portal vein gets divided into a right branch and a left branch in the hilum of liver . these branches supply right side of the liver and left side of the liver respectively. The portal venules get drained into liver sinusoids, then hepatic veins drains into inferior vena cava.

Liver has a low resistance and a high compliance system of circulation which is capable to accommodate a very large volume of blood without increase in portal pressure substantially. Liver has double blood supply in the form of portal vein and hepatic artery which constitutes of 30% of cardiac output. Venous blood from portal veins forms around 75% of total blood flow in the liver.

Convergence of blood derived from portal vein and hepatic artery takes place in a special blood channel which is highly compliant known as hepatic sinusoids.

Hepatic arterial buffer response is a autoregulatory mechanism which maintains the total blood flow of the liver at constant level.

ANATOMY OF FORMATION OF PORTAL VEIN



Portal vein communicate with systemic veins at 5 points

1. At the gastro esophageal junction(cardia)
2. In anal canal formed between superior hemorrhoidal vein and middle hemorrhoidal veins
3. Between para umbilical veins and the veins that drain the abdominal wall at region of falciform ligament
4. Between venous bed of the spleen and the left renal vein
5. In the retroperitoneum

Great clinical importance lies at gastro esophageal junction from which varices develop.

At the gastro esophageal junction a 4 well defined zones of the intrinsic veins are formed. They are

1. Gastric zone
2. Palisade zone
3. Perforating zone
4. Truncal zone

Gastric zone

It consists of a radially arranged band of veins in lamina propria and submucosa and is a 2-3 cm zone whose upper border lies at the gastro esophageal junction.

Palisade zone

Is a direct continuation of gastric zonal veins which takes origin at GE junction and run in palisading fashion or array of veins which are longitudinally packed in the region of lamina propria. They form the primary site of inter communication between the azygous and the portal bed.

Perforating zone

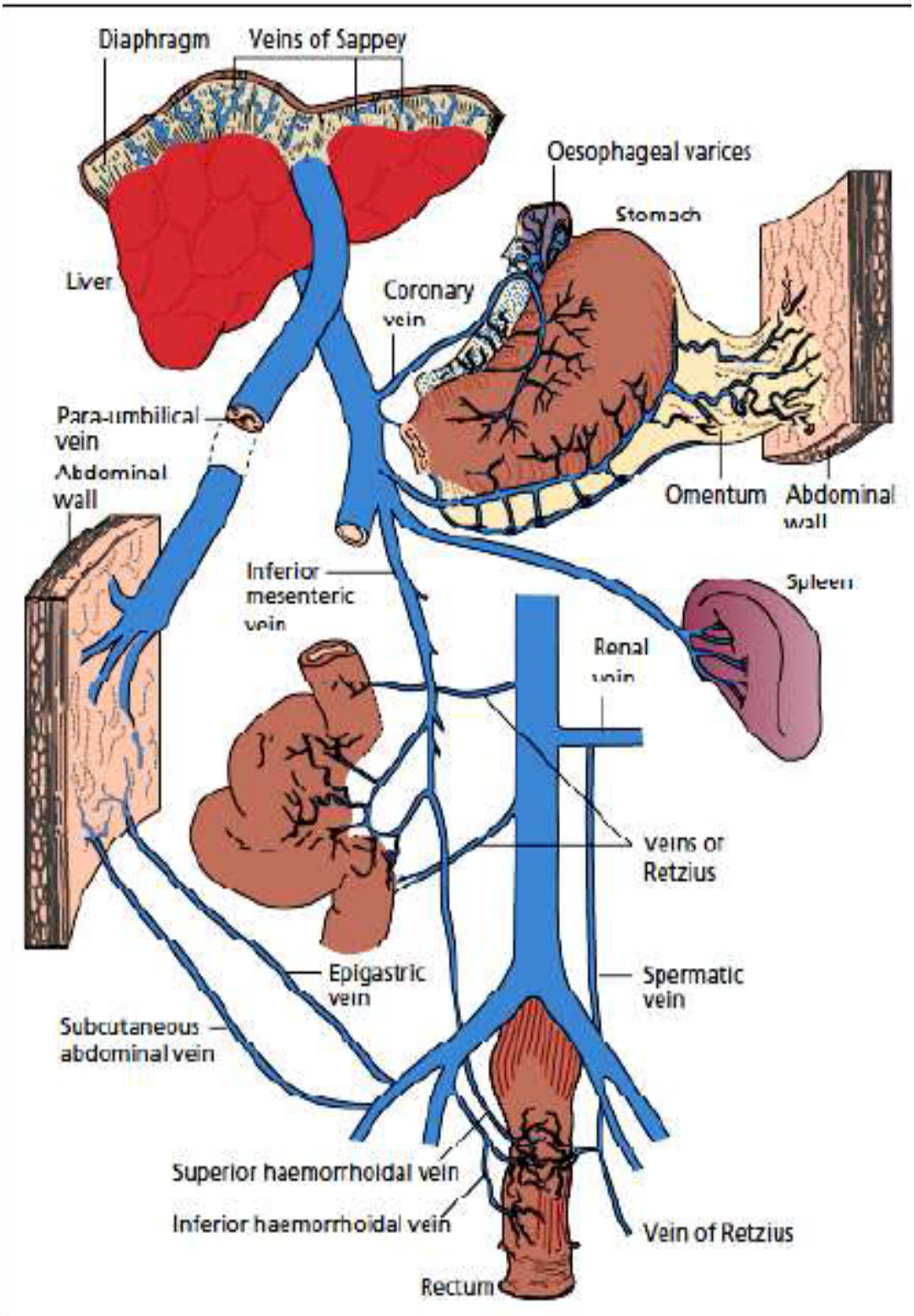
Is a 2-3 cm cranial extension of the palisade zone. The primary drainage of intrinsic veins into the extrinsic veins through the perforating veins which ahs valves. It normally permit uni directional flow.

Truncal zone

Is an eight to ten cm zone which continues from the perforating zone in an upward fashion. The intrinsic veins are made up of 3-4 large trunks of veins at the region of submucosa. It has a communication venous plexus of submucosal region. The direction of flow of is in a cranial to caudal fashion through the perforating veins into extrinsic venous channels.

In the situation of portal hypertension as an adaptive response increase in flow occurs to pump blood into the heart via the communication of porto systemic circulation. The intrinsic veins in and around the GE junction gets dilated and turns tortuous and they form varicose veins.

PORTOSYSTEMIC COMMUNICATIONS



PATHO PHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension is considered as one of the major complication of liver cirrhosis. Portal venous pressure greater than 12 mmHg is associated with development of clinical features or complication of cirrhosis of liver.

Normal physiology[13]

The passage of portal blood across the hepatic tissue depends mainly on the pressure gradient among the hepatic veins and the portal veins. Hepatic venous pressure is a reflection of central venous filling pressure. The product of blood flowing through the portal veins and the vascular resistance determines the portal pressure.

Portal pressure = portal blood flow x vascular resistance

The difference between the hepatic venous pressure and the portal venous pressure does not raise above 4 mmHg , under normal circumstances. In order to maintain the hepatic pressure gradient in a normal range ,the liver acts as a reservoir of blood.

To accommodate any alteration like increase in outflow pressure, the hepatic sinusoids are recruited in large numbers. Hence any elevation in hepatic venous pressure does not cause increase in portal pressure in similar manner.

Liver sinusoids acts as major site of resistance for portal vasculature.

The sum of the blood flow from the three major splanchnic tributaries forms Portal venous inflow.

In an normal individual 600- 1200 ml/ min is the normal portal inflow which is measured by Doppler flowmetry intra operatively.

The vascular resistance of the arteries of splanchnic circulation regulates the portal flow volume[21]. In case of physiological events like during postprandial state or any postural change, alteration of arteriolar resistance of splanchnic circulation will result in alteration of portal inflow. Somatostatin which is an inhibits many GI hormones which might mediate the arteriolar vasodilatation can be pre administered to prevent any rise in portal pressure after a meal. After a meal an increase in AV extraction of oxygen will result in reduction of oxygen content of the portal venous system.

HEMODYNAMICS IN PORTAL HYPERTENSION

Vascular resistance[22]

The development of portal hypertension is the result of rise in vascular resistance of portal circulation and this forms the basis of classification of portal hypertension. The combination of measurement of hepatic vein pressure and portal venous pressure gives an idea of site of vascular resistance in cirrhosis of liver. In non alcoholic cirrhosis many measurements will result in high pressure in portal veins when compared to hepatic venous wedge pressure.

This is an indication of existence of a pre sinusoidal component which may be related to the fibrotic changes or inflammation in the portal triads. Since the hepatic and portal venous wedge pressures remain same in alcoholic cirrhosis, the vascular resistance should lie at the level of sinusoids.

In case of alcoholic cirrhosis there lies a controversy in the pathogenesis of increase in sinusoidal resistance. Increase in sinusoidal resistance may be due to

- Presence of collagen in the space of Disse
- Los of fenestration in the sinusoids
- Existence of contractile myo fibroblasts
- Low resistance channel may become capillarized

In alcoholic liver disease a relationship between intrahepatic pressure and size of the hepatocyte was observed for a mild to moderate rise in pressure. A complex relationship lies between these factors in case of non alcoholic cirrhosis.[23]

Portal blood flow and systemic circulation

Two models are enlisted tin order to explain the changes of portal blood flow with response to PHT. The hypotheses are

- Backward flow hypothesis
- Forward flow hypothesis

Backward flow hypothesis

Is based on the fact that an increase in portal venous pressure which may trigger a myogenic response which in turn may decrease inflow into thesplanchnic arteries. Portal pressure will revert to normal as a result of this. The backward component may contribute to the maintenance of PHT even when it is established fully.

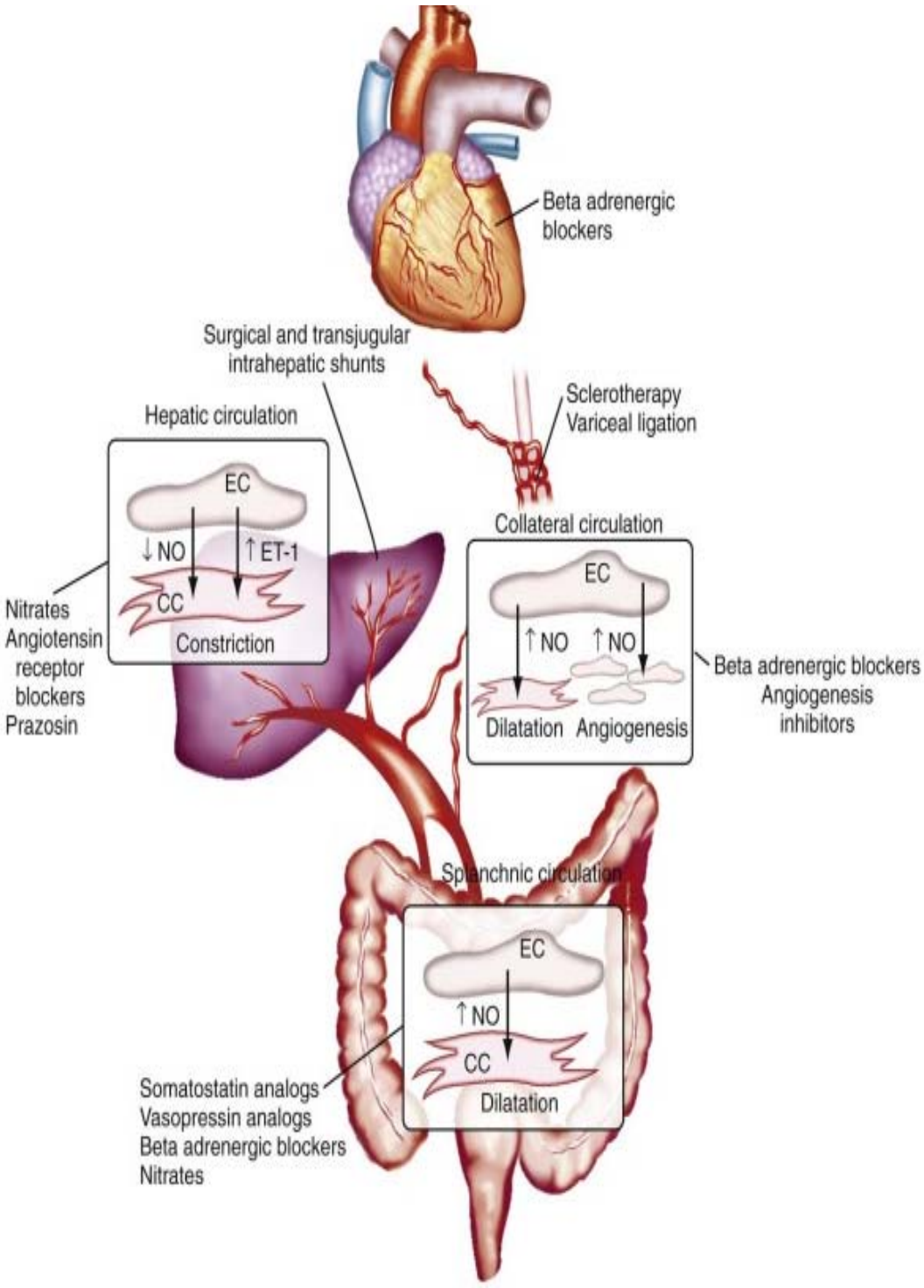
Forward flow hypothesis

The maintenance of portal hypertension is due to the paradoxical rise in portal inflow. Portal hypertension is a unique hemodynamic syndrome to exhibit both increase in resistance and increased inflow. [24-28]

The major factors which lead to fall in systemic vascular resistance are decrease in muscular arterial resistance and the resistance in the splanchnic circulation.

In various forms of portal hypertension a hyperdynamic circulatory state is observed. Peripheral vasodilatation may be due to humoral fectors. A rise in glucogan values is observed in the presence of PHT and porto systemic shunts. Prostaglandins, endotoxin mediated activation of NO, prostacyclin and bile salts are the other probable humoral factors.

VASCULAR DISTURBANCES IN PORTAL HYPERTENSION AND SITES OF ACTION OF DRUGS



PORTAL HYPERTENSION AS A HEMODYNAMIC SYNDROME

Splanchnic hemodynamics

- Increase in resistance of portal vasculature
- Increase in portal venous inflow
- Porto systemic shunting

Systemic hemodynamics

- Arterial vasodilatation
- Increase in plasma volume
- Reduction in systemic vascular resistance
- Increase in cardiac output
- Reduction in mean arterial pressure
- Rise in heart rate

Regional blood flows

- Reduction in cerebral blood flow
- Increase in blood flow to muscles
- Variations in blood flow to kidneys

Alterations in the blood flow volume can produce alterations in vascular resistance of the collateral bed. An increase in blood flow may increase diameter of the vessel and a decrease in blood flow may result in reverse changes with a small vessel which offers an rise in resistance to flow.

In a non distensible vessel the resistance to the flow of fluid is related to

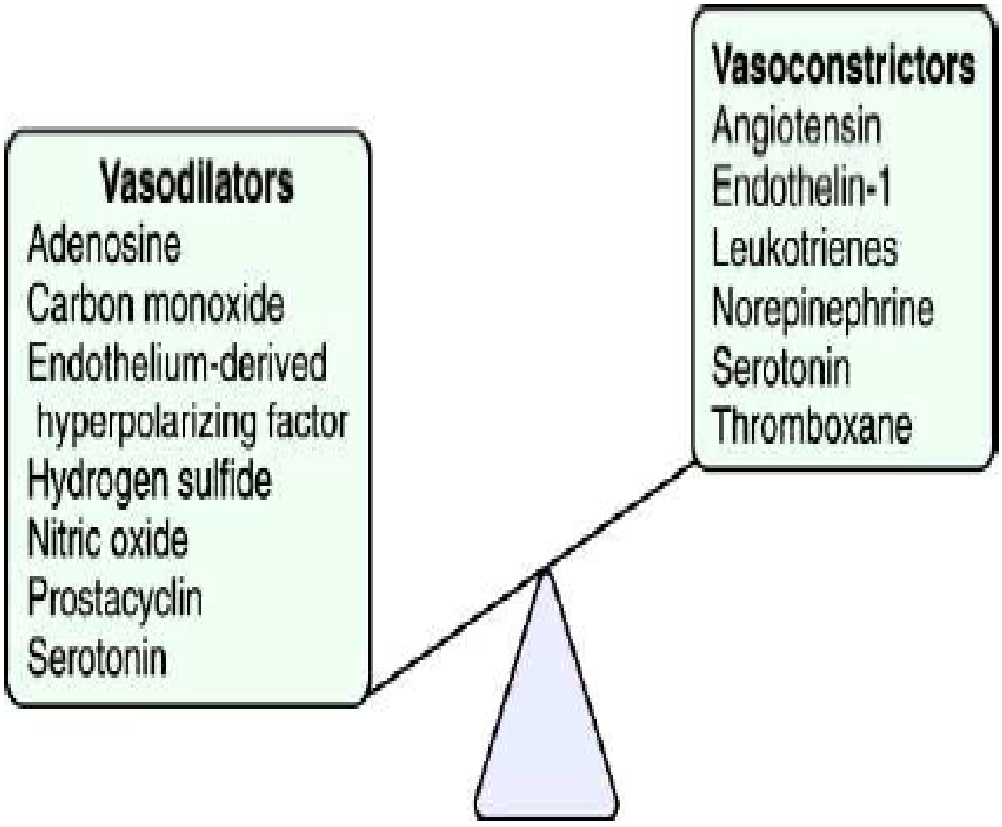
- The length of the vessel
- Viscosity of the fluid
- Inversely related to further power of the radius

Which leads to affect the resistance to flow markedly even during minimal changes in diameter of the vessel [poiseuille's law]

Resistance = 8nlπr4

Many drugs used in the treatment of PHT decrease portal pressure by decreasing the portal blood flow. The relationship among vessel flow and the radius of the vessel has been delineated denotes that a decrease in flow may lead to increase in vascular resistance. This is a significant principle in the drug therapy of portal hypertension.[25]

VASODILATOR AND VASOCONSTRICTOR MOLECULES IMPLICATED IN THE VASCULAR ABNORMALITIES IN PORTAL HYPERTENSION



RUPTURE OF ESOPHAGEAL VARICES[28-32]

The exact mechanism by which esophageal varices get ruptured has not been fully elucidated.

The " corrosion hypothesis" States that injury to the mucosa of the esophagus at the lower part with consequent erosion into the submucosal varices is due to the reflux of gastric acid.

Limitation : failure to exhibit the evidence for raised gastro esophageal reflex by measuring pressure at lower esophageal sphincter and pH.

Explosion hypothesis

States that esophageal rupture occurs when the vessel wall tension reaches a critical level.

A relationship between variceal pressure and bleeding risk has been documented by measuring variceal pressure by means of endoscopic capsule.

IMPACT OF PORTAL HYPERTENSION ON OTHER ORGANS

Hypersplenism can occur in spite of absence of splenomegaly. Others are

- ✓ Variation in the microcirculation the spleen
- ✓ Splenic sinusoids undergo fibrotic changes
- ✓ Entrapment of RBCs, white blood cells, platelets

Bonemarrow: remains active. In the absence of other factors that can cause alteration in platelet count like alcohol, drugs, thrombocytopenia is an indicator of portal hypertension.

Hypoxemia is an usual finding with partial pressure of arterial oxygen in the range of 60- 80 mmHg. The basic problem lies in the Pulmonary AV shunting Pulmonary hypertension may develop in some of the patients irrespective of the etiology of portal hypertension.

CLASSIFICATION OF PORTAL HYPERTENSION

PRE HEPATIC

- Portal vein thrombosis
- Splenic vein thrombosis
- Banti's syndrome (massive splenomegaly)

HEPATIC

Pre sinusoidal

- Schistosomiasis
- Congenital hepatic fibrosis

Sinusoidal

- Cirrhosis – many causes
- Alcoholic hepatitis

Post sinusoidal

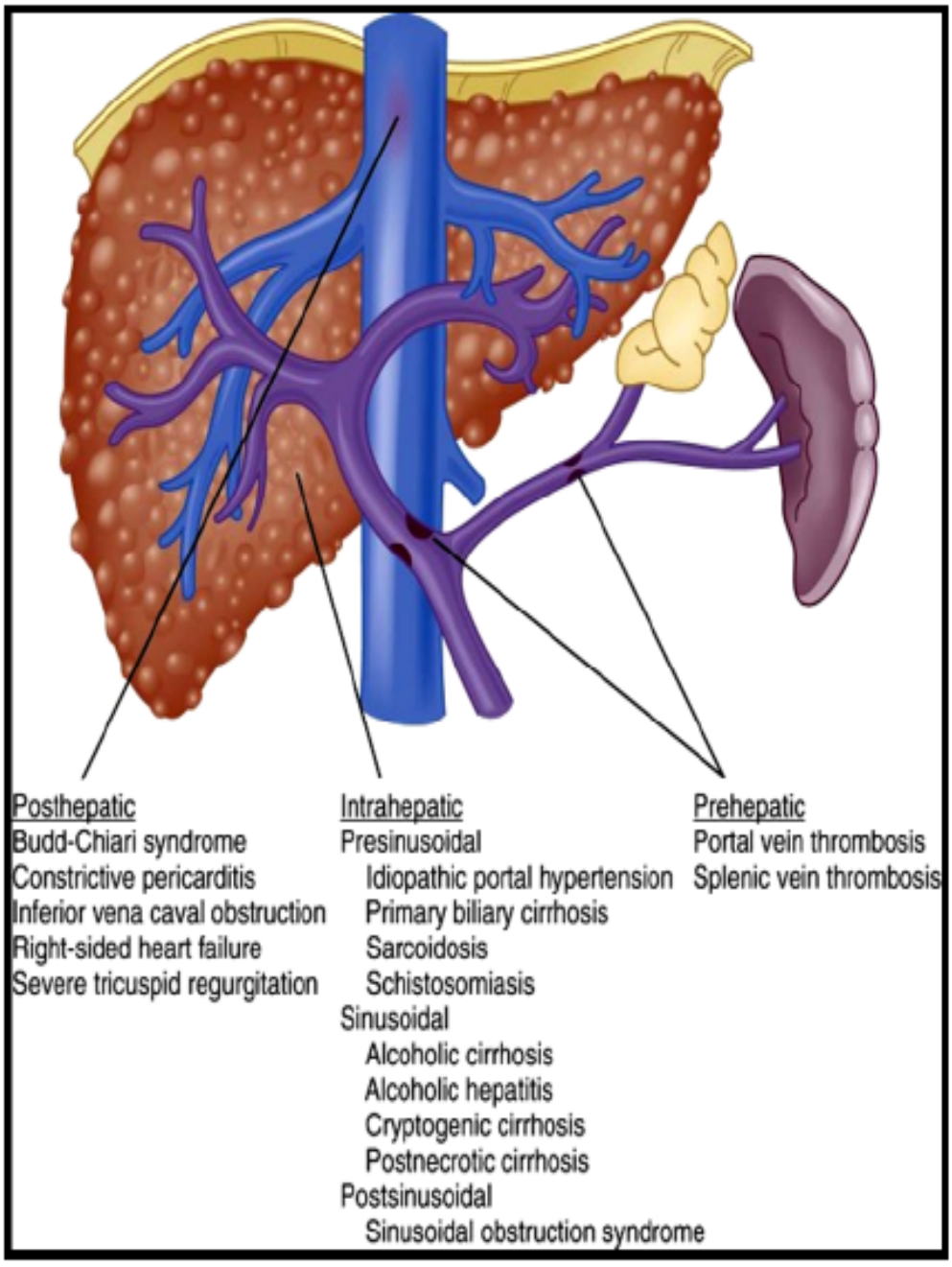
- Veno occlusive syndrome

POST HEPATIC

- Budd chiari syndrome
- Inferior vena caval webs
- Cardiac causes – restrictive cardiomyopathy, CCF Constrictive pericarditis

Prehepatic causes are those entities which affect the portal venous system before entering into the liver.

CLASSIFICATION OF PORTAL HYPERTENSION



Posthepatic causes are those entities which interfere with hepatic veins and venous drainage to the cardiac tissue.

Intrahepatic causes contribute to more than 95% of cases of portal hypertension , represented by common forms of cirrhosis.

COMPLICATIONS

Three major complications are gastro esophageal varices , ascites and hypersplenism. so patients present with

- ❖ Hemetemesis, malena
- ❖ Abdominal distension , pedal edema
- ❖ Splenomegaly
- ❖ Thrombocytopenia
- ❖ Leucopenia

Physical examination

May provide some clues to the differential diagnosis.

In the setting of variceal hemorrhage , always cirrhosis should not be presumed and other etiology such as pre sinusoidal may be taken into account. But pre sinusoidal etiology can be considered less likely if patient present with portal hypertension and ascites, until hypoalbuminemia may alter the relationship of hydrostatic pressure and the oncotic pressure of the capillaries of the intestine.

Liver size

Offers clues to narrow down the etiology. In the presence of portal hypertension a small liver suggests hepatic cirrhosis. Consistency of liver edge if it is found to be normal, it can less likely to be a sinusoidal etiology.

Venous hum

Excludes portal vein thrombosis if it is present in the peri umbilical area which indicates high flow via aa patent umbilical vein.

IMAGING OF THE PORTAL VENOUS SYSTEM [10-13]

CHEST RADIOGRAPHY

An enlarged and distended azygous vein may present in chest x ray which may be interpreted as a mass in right hilar area or there may be an enlarged pulmonary arteries.

ANGIOGRAPHY

Angiography of the mesenteric vessels may give some physiological and anatomical data. Splenoportography provides excellent anatomical detail but rarely used because of risk of puncture to the spleen.

ULTRASONOGRAPHY

An enlarged portal vein may be suggestive of portal hypertension. If collaterals are visualized it may confirm the presence of portal hypertension.

DOPPLER ULTRASONOGRAPHY

Doppler ultrasonogrphy may portray the anatomical details of the hepatic artery and the portal vein.

It may depicts the spontaneneous hepato fugal flow in the portal vein, splenic vein and superior mesenteric vein in cirrhotic patients.

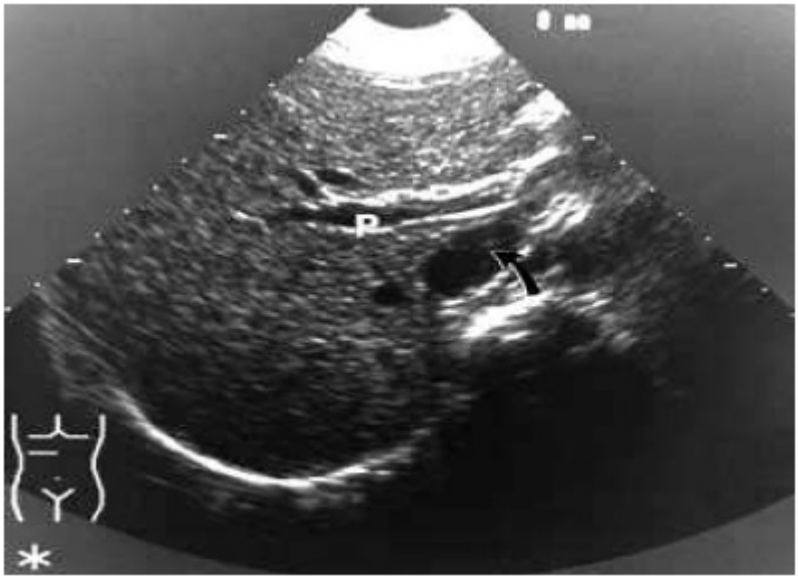
If the flow is in ahepato petal direction there may be a possibility of variceal hemorrhage.

COMPUTED TOMOGRAPHY

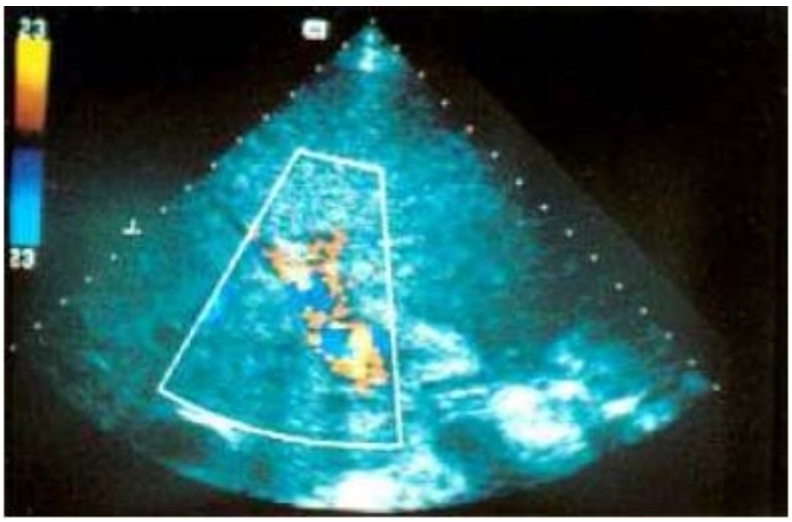
A contrast CT scan may portray the patency of the portal vein ane the esophageal varices as an protruding intraluminal shadows which gets enhanced after a contrast.

Gastric varices may be seen as rounded structures which are not differentiated from the gastric wall.

The venogram shows a wide variation in the presence of cirrhosis "Tree in winter appearance" – filling of large collateral vessels with distortion of intra hepatic pattern grossly.



Ultrasonography shows a patent portal vein(P); arrow indicates inferior vena cava



COLOUR DOPPLER ULTRASONOGRAM OF THE PORTA HEPATIS SHOWS THE HEPATIC ARTERY IN RED AND PORTAL VEIN IN BLUE

SCREENING FOR VARICES

All cirrhotic patients should undergo screening for esophageal varices in order to provide prophylactic treatment to those patients who are at increased risk of hemorrhage.

RATIONALE:

Improved clinical outcomes are observed with identification and treatment of patients with high risk varices.

At the time of diagnosis 30% of compensated cirrhotic patients and 60% of decompensated cirrhotic patients found to have varices.

Among the patients with varices, 12% is the annual rate of first bleeding episode and the mortality rate after each episode of bleeding is 15 – 20 %.

SCREENING METHODS

- OGD scopy : it is the gold standard method
- VIDEO CAPSULE ENDOSCOPY

Screening is repeated every 2 – 3 years in compensated cirrhotic patients who do not present with varices. Screening is repeated every year or at the time of 1st decompensation in patients with decompensated cirrhosis.

PARAMETERS ASSESSED are

a) Number of varices

b) Appearance

c) Size of esophageal varices

d) Presence of red color signs

CLASSIFICATION OF VARICES[4]

- F1: Small, Straight Varices
- F2: enlarged , tortuous varices that occupy < 1/3rd of the lumen
- F3: large, coil-shaped varices that occupy > 1/3rd of the lumen

Many hepatologists and endoscopist categorize varices as either large or small, since medium sized varices F2 are managed same way as large varices F3.

PROGRESSION OF VARICES [23-28]

The rate of development of and progression of esophageal varices has not been evaluated extensively in cirrhotic patients. Based on a clinical trial the following were noted from annual endoscopy.

- New varices develop in 5 % at one year, 28% at the 3rd year
- Small varices progressed in size at a rate of 12% in 1st year and 31% in 3rd year

- Progression was predicted by child pugh score, presence of red wale signs on the 1st examination and an alcoholic cause of cirrhosis

- The 2 year risk of bleeding was significantly high in patients with small varices than without varices.

- For patients with compensated cirrhosis and NO varices –repeat endoscopy is recommended every 2-3 years. For patients with small varices OGD is repeated every 1-2 years

VARICEAL BLEEDING

Active variceal bleeding accounts for about 1/3rd of all deaths related to cirrhosis. There are 4 major issues with respect to prevention and treatment of variceal bleeding

- ❖ Prediction of at risk patients
- ❖ Prophylaxis against a 1st episode of bleed
- ❖ Treatment of active bleed
- ❖ Prevention of re bleeding

PREDICTIVE FACTORS [12]

- ➢ Location of varices
- ➢ Size of varices
- ➢ Appearance of varices
- ➢ Clinical features of the patient
- ➢ Variceal pressure

Location of varices:

The most common sites are distal end of esophagus, stomach, rectum. Varices arise deep within the submucosa in the mid esophagus but becomes superficial at the distal end of esophagus.

Size of the varices

The risk of variceal hemorrhage correlates independently with diameter of the varix.

Appearance of varices

RED SIGNS

- Red wale marks: longitudinal red coloured streaks on varices that are similar to red corduroy wales
- Cherry red spots : discrete red cherry coloured spots which are flat and lie above the varices
- hematocystic spots : elevated discrete spots that are similar to blisters
- Diffuse erythema: diffuse red color of varix

Clinical features

- Degree of hepatic dysfunction
- History of previous variceal hemorrhage

Variceal pressure

The incidence of variceal hemorrhage with different variceal pressure levels are

- <13 mmhg – 0%
- >13 mmhg – 9%
- >14- 15mmhg – 17%
- >15- ≤16 mmhg – 50%
- >16 mmhg - 72%

PRIMARY AND PRE- PRIMARY PROPHYLAXIS [35-39]

Pre primary prophylaxis

Aims at preventing the development of varices in patients with portal hypertension who have not yet developed varices. These patients are to be routinely screened for detecting development of varices.

Primary prophylaxis

Refers to the prevention of first variceal bleeding in a patient with varices. The approaches are

PHARMACOLOGICAL PROPHYLAXIS:[32-36]

Using a non selective beta blocker propronolol and nadolol. The goal of drug therapy is to reduce the portal venous inflow. These non selective beta blockers will block the adrenergic dilatory tone in mesenteric arterioles, which results in unopposed alpha mediated vasoconstriction which results in reduction of portal inflow.

The dose of NADOLOL : 40 mg per day

PROPRANOLOL : 20 mg twice daily

Propranolol produce a 9 -23% reduction in HVPG.

DOSE TITRATION for these drugs are achieved by

a) Titrating resting heart rate- to achieve arresting heart rate of 55 – 60 beats per minute.
b) HVPG : A decrease in HVPG below 12 mmhg probably eliminates the risk of variceal bleed.

ENDOSCOPIC PROPHYLAXIS

Using endoscopic variceal ligation

The general approach based on Baveno consensus and AASLD guidelines, the prophylaxis is given to patients with

- Small varices with red signs or child B or C cirrhosis
- Medium or large varices

EVL eradicates esophageal varices with fewer complications than endoscopic sclerotherapy.

Complications associated are bleeding from banding induced ulcerations. So EVL should be done by an endoscopist with expertise in prophylactic banding.

Approaches that are not advised for primary prophylaxis are

- Endoscopic sclerotherapy
- Surgical portal decompression
- Transjugular intrahepatic porto systemic shunts

TREATMENT OF ACTIVE VARICEAL HEMORRHAGE

The current treatment options available are

- Pharmacological therapy
- Endoscopy
- Surgery
- TIPS procedure

GENERAL PRINCIPLES OF SUPPORT

- Transfusion

  Prevention of aspiration

- Use of recombinant factors

PROPHYLACTIC ANTIBIOTICS

Cirrhotic patients presenting with upper GI bleeding should be given prophylactic antibiotic preferably before endoscopy.

The AASLD guidelines recommend the use of

- Oral norfloxacin 400mg twice daily

  I.V. Ceftriaxone 1g/ day is preferred in centres with quinolone resistant organisms.

INTRAVENOUS VASOPRESSIN AND ITS ANALOUGS

a) **Vasopressin :** dose 0.4 u bolus followed by 1 unit/ min infusion . it directly constricts mesenteric arterioles and reduces portal venous inflow and reduces portal pressure.

Limitations :

- will not improve survival from active hemorrhage
- Has very minimal effects on early rebleeding episodes
- Extra splanchnic vasoconstrictor property

b) **Terlipressin :** synthetic analog of vasopressin, released in slow and sustained manner

Dose : 2 mg IV every 4^{th} hourly titrated to 1 mg every 4^{th} hourly once bleeding is controlled.

SOMATOSTATIN AND ITS ANALOGS

Somatostatin causes inhibition of the liberation of glucogon, causing indirect vasoconstriction of splanchnic circulation and reduces portal blood flow. Since somatostatin is not widely available , its analog is used.

OCTREOTIDE

Long acting analog of somatostatin .

Given as 50 mcg bolus IV followed by 50 mcg per hour infusion and continued for 3 – 5 days.

ENDOSCOPIC TREATMENT

It is currently the definitive treatment of choice for active variceal bleeding.

Two forms commonly used are

- **Sclerotherapy:** injection of sclerosant solution into the varices through an injection needle that is placed through the endoscope using freehand technique.
- **Variceal Band Ligation**: it involves placing of elastic bands around the varices in the distal 5cm of esophagus.

FAILURE OF ENDOSCOPIC THERAPY

Defined as mortality or necessity to change treatment defined by

- New episode of blood vomiting or Ryles tube aspiration of greater than or equal to100ml of fresh blood. More than or equal to 2 hours after the initiation of particular drug therapy or therapeutic Endoscopy
- Development of hypovolemic shock
- 3 g fall in hemoglobin during any 24 hour duration if no transfusion is done.

BALLOON TAMPONADE

It is reserved for temporary stabilization of patients until more definitive treatment can be instituted.

3 balloons has been used

- Sengstaken – blackmore tube
- Minnesota tube
- Linton-nachias tube

Initial control of bleeding has been achieved in 30 – 90% of patients.

Major limitation: rebleeding following deflation.

SURGERY

Ideal patient for surgery : one with preserved liver function who fails emergent endoscopic treatment and has no complications from the bleeding or endoscopy.

TYPES OF SURGERY[42]

SHUNT OPERATIONS

Categorized as

- Non selective : portocaval shunts
- Selective : distal splenorenal shunt
- Partial

NON SHUNT OPERATIONS

- Esophageal transaction
- Devascularisation of gastroesophageal junction – suglura procedure

TRANSJUGULAR INTRAHEPATIC PORTO SYSTEMIC SHUNTS

A TIPS is created by passing needle catheter via the transjugular route into the hepatic vein and wedging it there. The needle is then extruded and advanced through the liver parenchyma to intrahepatic portion of tha portal vein . It is indicated for patients with uncontrolled variceal bleeding despite combined drug therapy and endoscopic therapy.

RECURRENT VARICEAL BLEEDING

AASLD GUIDELINES

- Cirrhotic patients who survive an episode of active variceal bleeding should get therapy for secondary prophylaxis
- Combination of non selective beta blockers and endoscopic variceal ligation is the best method for secondary prophylaxis
- EVL should be done once in 1 to 2 weeks till it gets obliterated
- TIPS should be considered in patients with child A or B cirrhosis and underwent recurrent hemorrhages inspite of combination of drug therapy and endoscopic treatment.

- ❖ Patients who are eligible to undergo transplatation should be referred to a centre with facility for transplantation.

NON INVASIVE PARAMETERS FOR PREDICTION OF ESOPHAGEAL VARICES

Studies have attempted to identify parameters that non invasively predict the presence of esophageal varices.

Overall the most common results of these studies , the parameters are splenomegaly and thrombocytopenia.

More recently transient elastography (fibroscan) which estimates liver stiffness(LS) , has been a new method to diagnose esophageal varices with cirrhosis non invasively. While the accuracy of fibroscan in predicting clinically significant portal hypertension is good, its discriminative ability of predicting varices needs further validation.

In a study by Thomopoulus et al(2003) seventeen variables considered relevant to the presence of esophageal varices were tested and came to conclusion that thrombocytopenia, splenomegaly and ascites are independent predictors of large esophageal varices in cirrhotic patients. The author suggest that OGD scopy could be withheld safely in cirrhotic patients with none of these predictive factors, as large varices are absent in this group of patients.

Sharma SK et al[49] in a prospective study took account of patients who are diagnosed for the first time with cirrhosis and no history of hemorrhagic episodes were scheduled to subjected for OGD scopy. Of the 101 patients (median age 45; range 15-74 years; 87 male; Child-Pugh class: A 18, B 31, C 52), 46 had LEV. On univariate analysis, 5 variables were significantly associated with thepresence of LEV. These included anaemia (P = 0.026), splenomegaly(P= 0.009), platelet count (P < 0.002), total WBC count (P0.0004) and liver span on ultrasound (P = 0.031). On multivariate analysis, 2 of these parameters, thrombocytopenia and splenomegaly, were identified as independent predictors of the presence of LEV. The conclusion made was that presence of splenomegaly and thrombocytopenia are independent predictors of presence of LEV in cirrhotic patients. With the help of these parameters, may identify patients with a low probability of LEV who may not need UGIE. This may help decrease economic burden and displeasure for these patients and the workload of OGDscopy units.[49]

Zaman A et al47 studied ninety-eight patients without a history of variceal hemorrhage underwent esophago gastroduodenoscopy as part of a liver transplant evaluation. The etiology of cirrhosis among the 67 men and 31 women (mean age, 48 yr) included 28% viral HepatitisC infection ,ethanol consumption, 25% viral Hepatitis C, 13% , 9% primary

sclerosing cholangitis/primary biliary cirrhosis, 9% cryptogenic, 6% Hepatitis B, 1% Hepatitis B and C, and 9% other.

Patients were Child-Pugh class A 34%, B 51%, and C 15%. Endoscopic findings included esophageal varices in 68% of patients (30% were large), gastric varices in 15%, and portal hypertensive gastropathy in 58%.

Platelet count <88,000 was the only parameter identified by univariate/multivariate analysis ($p < 0.05$) as associated with the presence of LEVs (odds 55 ratio 5.5; 95% confidence interval 1.8-20.6) or gastric varices (odds ratio 5; 95%confidence interval 1.4-23). Platelet count <88,000 is associated with the presence of esophagogastric varices. A large prospective study is needed to confirm and validate these findings and may allow identification of a group of patients who would most benefit from OGD scopy screening for varices.

RELEVANCE OF PLATELET COUNT/SPLENIC DIAMETER RATIO

Gianni et al (2003)[54] made a proposal that ratio of PC/SD ratio, as a non invasive tool for prediction of esophageal varices in patients with chronic liver disease.

In the study done by Gianni et al the largest diameter of spleen was Calculated with the help of ultrasonography and was read in

millimetres (mm).the ratio of PC/SD of all patient was computed. The results were that diameter of the splenic tissue was larger while PC/SD ratio was smaller value in patients with esophageal varices. Receiver operating characteristic curve (ROC curves) were [56] applied to tabulate the PC/SD ratio cut off which may give the results of the best sensitivity and specificity in diagnosing of esophageal varices (cut off=909, sensitivity=100% (95% CI 100–100); specificity=93% (95% CI 82–98)).

The prevalence adjusted positive and negative predictive values were 96% and 100% corresponding, for a ratio of PC/SD of 909. furthermore , accuracy of the ratio of PC/SD cut off value as calculated by the *c* index was 0.981 (95% CI 0.943– 0.996).

Gianni et al (2003)[54] stated that the application of this ratio is of significant and is useful , and this hypothesis can be given support by a numerable clinical and statistical causes.

However , the value of the PC/SD ratio overcome this probable disadvantage because it "normalizes" platelet count to splenic sequestration, invariably representing the aliquot of reduction in platelet count resulting from portal hypertension.

Moreover , from a statistical point of consideration, the PC/SD ratio was the one variable independently associated with the presence of esophageal varices.

The study suggested that the value of the platelet count/spleen diameter ratio may avoid conducting OGD scopy that is not needed in all patients with a cut off >909 without meeting the risk of undiagnosed of esophageal varices. It is cost benefit also.

According to Gianni et al (2005)[64] after the 1st OGD scopy, the value of the PC/SD ratio found as an efficient means for identification of the presence of oesophageal varices in the longitudinal follow-up of cirrhotic patients also.

WW Baig et al[65] conducted a study involving 150 patients of chronic liver diaease by making use of Lab and USG parameters as a prospective study. The platelet count/ spleen diameter ratio in patients with esophageal varices were statistically significant.

Abu El Makarem MA et al conducted a prospective study from that they cocluded that the platelet count/ bipolar spleen diameter ratio has excellent accuracy in the non invasive assessment of EVs in cirrhotic patients.

RELEVENCE OF FIBROSCAN [55 – 59]

FIBROSCAN (transient elastography) is a novel and a promising approach for staging hepatic fibrosis. It rapidly and non invasively measures the mean hepatic tissue stiffness.

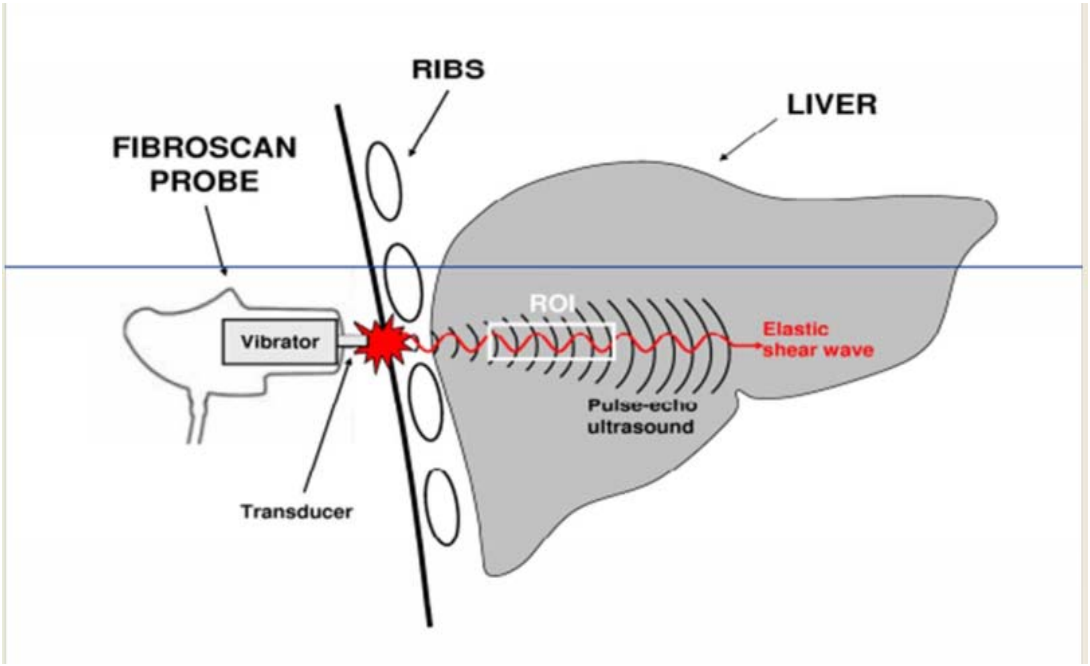
Using a probe, which includes an ultrasonic transducer , a vibration of low frequency (50 MHz) and amplitude is transmitted into the liver. The vibration wave induces an elastic shear wave that propagates through the organ. The velocity of this wave as it passes through liver correlates directly with tissue stiffness. The harder the tissue, the faster the shear wave propagates. Results are expressed in kilo pascals.

Fibroscan measure liver stiffness of a volume that is approximately a cylinder of 1 cm diameter and 5 cm long, which is 100 times greater in size of a standard liver biopsy and thus may be more representative of liver parenchyma.

FIBROSCAN

XL PROBE- NEW ADVANCEMENT

MECHANISM OF FIBROSCAN



ADVANTAGES

- The scan can be easily performed.
- It is an inexpensive tool.
- It does not produce any side effects
- Patient may feel the pressure of the probe without anticipated pain.
- The measurement can be reproducible
- It is independent of the operator.

LIMITATIONS

The following parameters may hamper the accuracy of the test

- Obesity
- Tense ascites
- Narrow intercostal space

RATIONALE OF FIBROSCAN

Fibroscan may be used as a indirect tool to assess the presence of portal hypertension.

Presence of large esophageal varice s can be predicted by measuringthe lver stiffness in cirrhotic patients and may assist in selecting patients for OGDscopy screening.

Foucher et al studied the importance of TE for detecting large esophageal varices and the variceal hemorrhage risk in patients with cirrhosis. For stage 2 esophageal varices the LS value was 27.5 kPa and for stage 3 it was around 62.7 kPa.

It was concluded that fibroscan may be of great use in the management and follow up of the patient.

Klibansky et al was successful in describing a valuable application of fibroscan to predict clinical outcomes in cirrhosis.

Castera et al had a conclusion that fibroscan can be a promising tool for prediction of esophageal varices and discriminates the patients with large esophageal varices with the risk of bleeding. However optimal cut offs may vary from study to study an optimal fibroscan cut off remains to be defined.

Sporea et al ., studied 1000 patients with cirrhosis and the optimum cut off value for presence of varices was 31 kPa and for bleding cut off was 50.7 kPa.

Vizzutti et al showed a cut off value of 17.6 kPa for prediction of varices.

Based on these studies we wanted to evaluate for the prediction of esophageal varices in chronic liver disease using fibroscan and other

parameters like platelet count and spleen size taking into the ratio of platelet count is to the spleen diameter.

MATERIALS AND METHODS

Study design : Observational study

Study centre : Madras medical college & Rajiv Gandhi Government General Hospital Chennai-600003

Duration of the study : 6 months

Ethics Committee Approval : Obtained

Inclusion criteria: Newly diagnosed chronic liver disease patients irrespective of the etiology

Exclusion criteria

- Patients who received endoscopy previously for variceal bleeding
- Patients with hepatocellular carcinoma
- Patient who has undergone surgical intervention for portal hypertension
- Patients with Post hepatic causes of cirrhosis

Sample size : 50

INVESTIGATIONS DONE

- Complete hemogram
- Hemoglobin (g/ dl)
- Total count (cells/ cumm)
- Differential count
- RBCs
- Platelet count
- MCV
- MCHC
- PCV

Renal function tests

- Blood urea
- Serum creatinine
- Plasma glucose

Liver function tests

- Total bilirubin
- Direct bilirubin
- SGOT
- SGPT
- ALP
- Total protein
- Serum albumin

USG abdomen

Spleen size

Ascites : yes/ no

Chest radiography

Fibroscan

Upper GI Endoscopy

Spleen platelet ratio

PROCEDURE

Fifty patients with chronic liver disease , attending medical ward, hepatology ward and out patient department of Rajiv Gandhi Government General hospital , Chennai, between the month of March 2014 to September 2014 were selected for observational study, based on the inclusion and exclusion criteria.

All patients in the study underwent a full clinical examination. Clinical history and physical examination findings were recorded with particular attention to present or previous history of hemetemesis, malena, bleeding per rectum, bleeding diathesis, alcohol intake, blood transfusion, intake of hepatotoxic drugs, exposure to sexually transmitted diseases, iv drug abuse, jaundice, anaemia, splenomegaly and encephalopathy.

All patients underwent biochemical tests, such as liver function tests, complete hemogram, renal function tests, prothrombin time, ultrasonography of the abdomen to confirm the presence of cirrhosis and to record spleen bipolar diameter, portal vein size, ascites and presence of collaterals.

Fibroscan was done to assess the stiffness of liver.

Fibroscan is done using in the morning with patients in a fasting state.

Measurements were performed using XL probe on the right lobe of the liver through through intercostals spaces on patient lying in the dorsal decubitus position with right arm in maximal abduction. The tip of the probe transducer was placed on skin between the ribs at the level of right lobe of the liver. Ten successful measurements are taken on each patient. Success rate was calculated as the ratio of number of successful measurements over the total number of acquisitions of which 60% is considered as best.

Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them.

Data were collected in a pre determined proforma and results were analysed using software statistical package student version. Continous

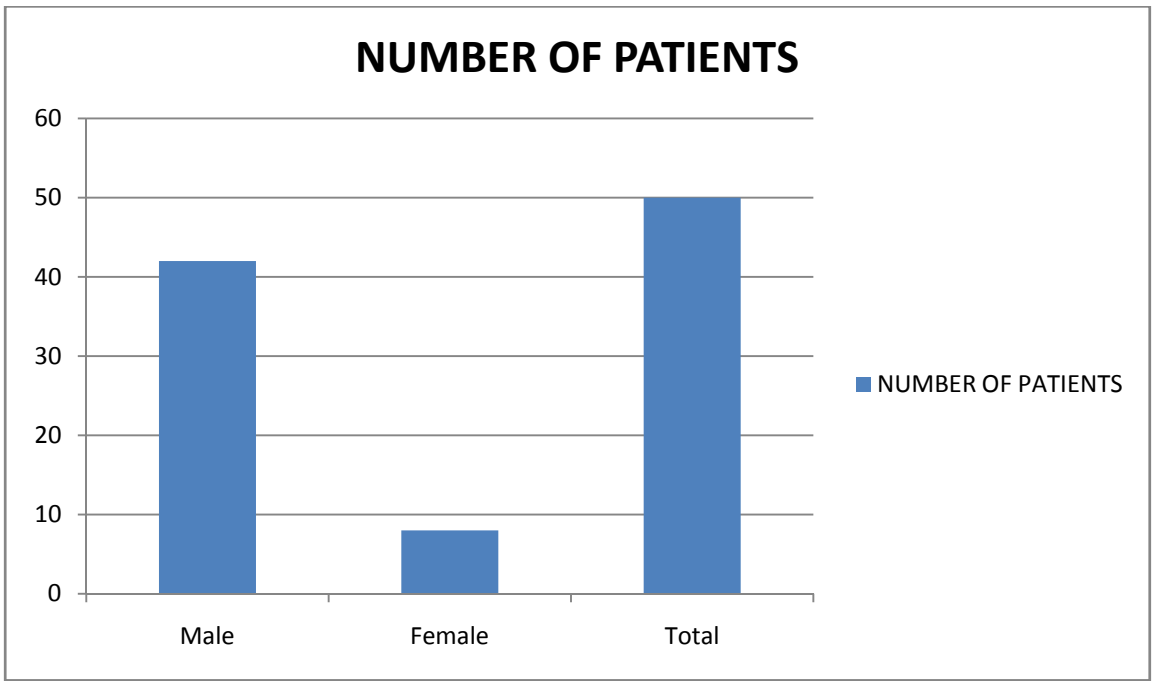
variables were analysed using t- test and categorical variables by chi square test . pearson correlation was used to find the correlation between two variables.The following results were obtained.

OBSERVATION AND RESULTS

SEX DISTRIBUTION

SEX	NUMBER OF PATIENTS	PERCENTAGE
Male	42	84
Female	8	16
Total	50	100

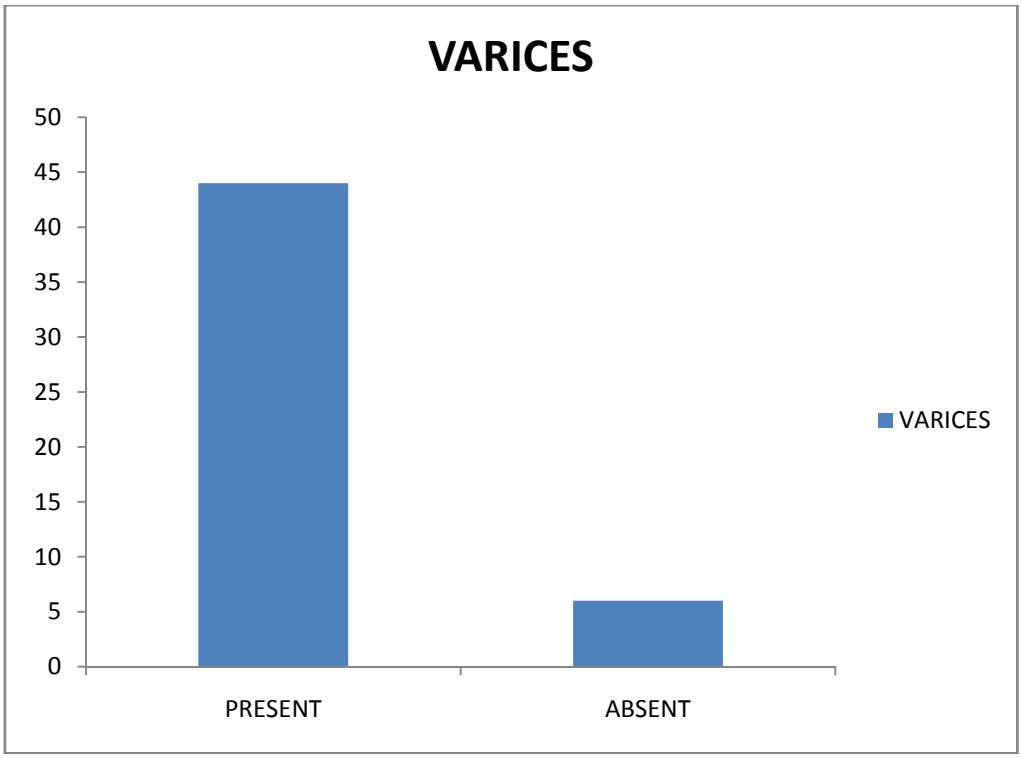
SEX DISTRIBUTION



PRESENCE OF VARICES AMONG PATIENTS

	Frequency	Percent
Positive	44	88.0
Negative	6	12.0
Total	50	100.0

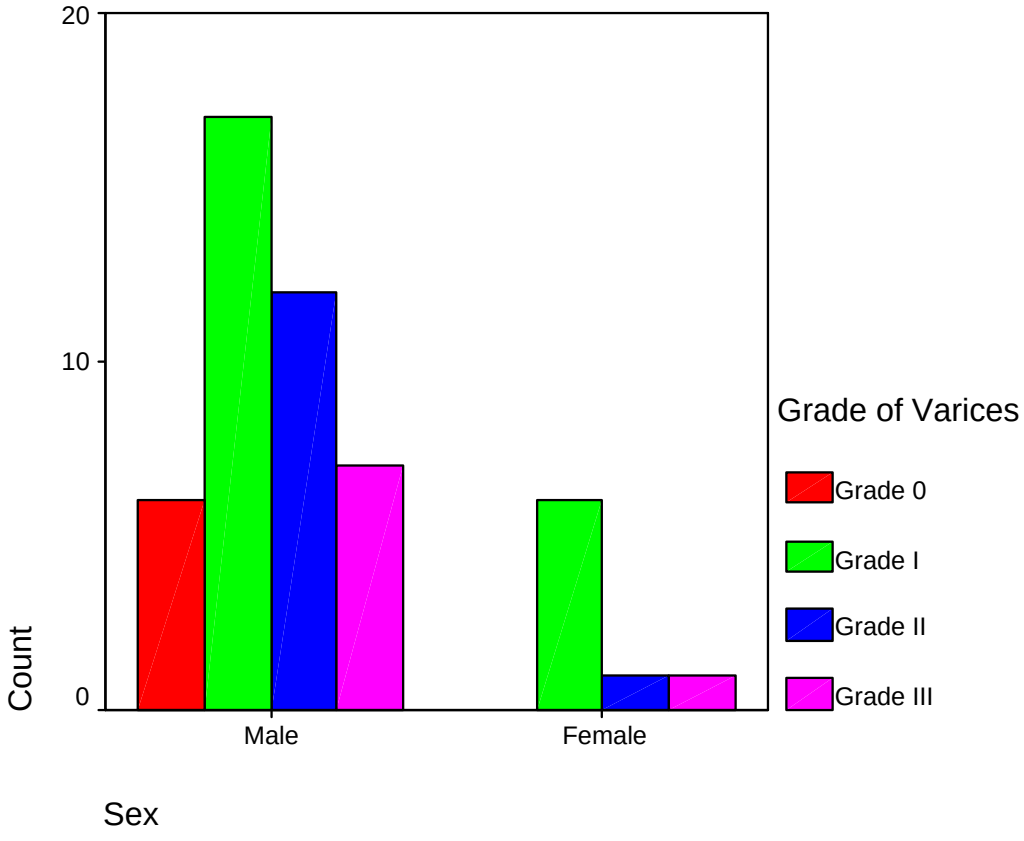
PRESENCE OF VARICES AMONG PATIENTS



GRADE OF VARICES

	Frequency	Percent
Grade 0	6	12.0
Grade I	23	46.0
Grade II	13	26.0
Grade III	8	16.0
Total	50	100.0

GRADE OF VARICES AMONG PATENTS



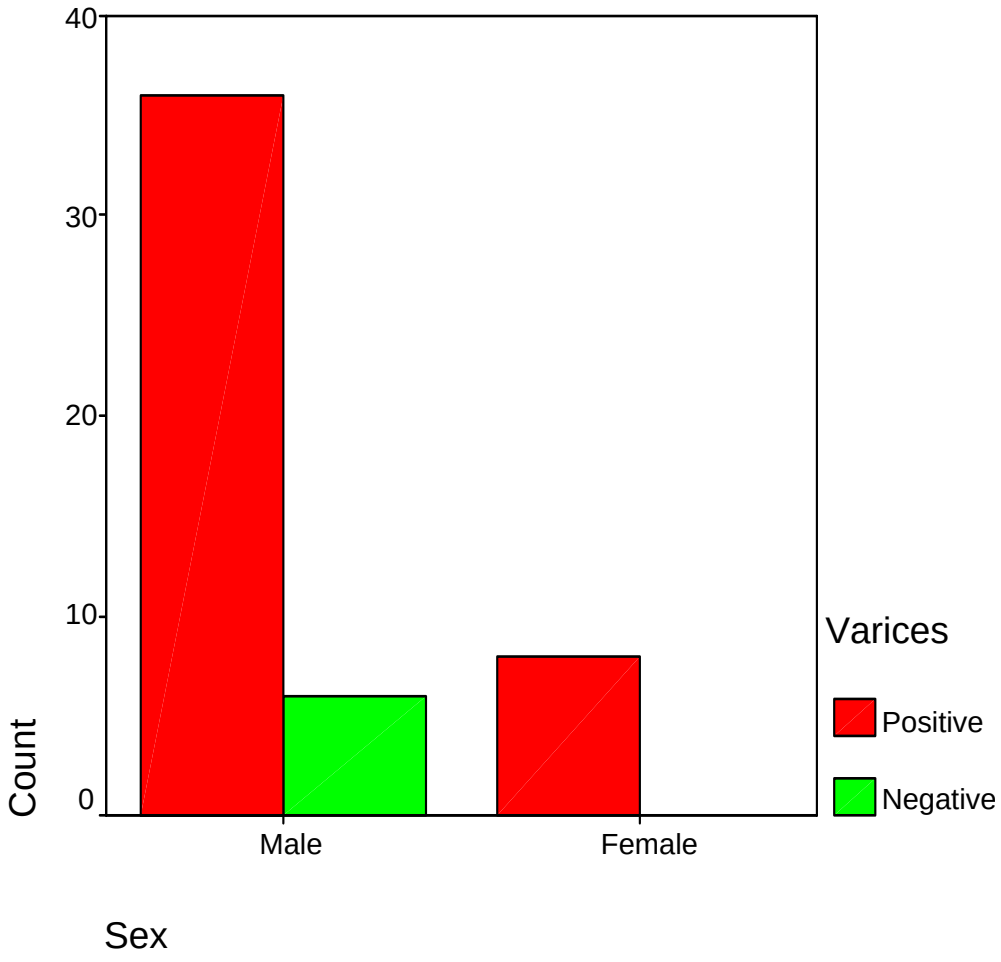
DESCRIPTIVE STATISTICS

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Age in years	50	46	18	64	45.28	10.852
HB%	50	9.8	5.1	14.9	11.030	2.1879
PT	50	45.0	14.0	59.0	23.850	8.4692
INR	50	2.98	1.05	4.03	1.8920	.64632
S.Bilirubin	50	36.9	.3	37.2	7.186	9.1926
S.Albumin	50	2.6	1.5	4.1	2.452	.4665
Platelet Count	50	334000	19000	353000	101852.00	62533.071
Spleen Bipolar Diameter	50	94	78	172	122.00	29.491
PC/SD Ratio	50	3379.21	150.79	3530.00	915.9412	659.15656
Fibroscan L.S	50	60.9	14.1	75.0	42.421	17.1934
Valid N (listwise)	50					

COMPARISON BETWEEN SEX AND PRESENCE OF VARICES

			Varices		Total	P value
			Positive	Negative		
Sex	**Male**	**Count**	**36**	**6**	**42**	0.254 (NOT SIGNIFICANT)
		% within Sex	85.7%	14.3%	100.0%	
		% within Varices	81.8%	100.0%	84.0%	
	Female	Count	8	0	8	
		% within Sex	100.0%	.0%	100.0%	
		% within Varices	18.2%	.0%	16.0%	
Total		Count	44	6	50	
		% within Sex	88.0%	12.0%	100.0%	
		% within Varices	100.0%	100.0%	100.0%	

COMPARISON BETWEEN SEX AND PRESENCE OF VARICES



PC/SD RATIO & FIBROSCAN L.S VALUE

	Varices	N	Mean	Std. Deviation	P value
PC/SD Ratio	Positive	44	758.7315	419.39005	**<0.001 (highly significant)**
	Negative	6	2068.8125	965.87447	
Fibroscan L.S	Positive	42	45.440	16.2323	**<0.001 (highly significant)**
	Negative	6	21.283	2.3267	

PLATELET COUNT AND PRESENCE OF VARICES

	N	Mean	Std. Deviation	Minimum	Maximum	P value
Grade 0	6	190000.00	104370.494	95000	353000	0.001 (Significant)
Grade I	23	97634.78	42005.785	31000	179000	
Grade II	13	85461.54	49765.476	19000	205000	
Grade III	8	74500.00	41572.656	31000	163000	
Total	50	101852.00	62533.071	19000	353000	

SPLEEN BIPOLAR DIAMETER AND PRESENCE OF VARICES

	N	Mean	Std. Deviation	Minimum	Maximum	P value
Grade 0	6	89.33	14.679	78	114	**< 0.001** (Highly Significant)**
Grade I	23	110.35	25.906	78	170	
Grade II	13	139.38	20.468	96	164	
Grade III	8	151.75	13.156	136	172	
Total	50	122.00	29.491	78	172	

PC/SD RATIO AND PRESENCE OF VARICES

	N	Mean	Std. Deviation	Minimum	Maximum	P value
Grade 0	6	2068.8125	965.87447	1186.05	3530.00	**< 0.001****
Grade I	23	908.6580	380.25870	182.35	1864.58	
Grade II	13	650.6636	458.42174	150.79	1863.64	**(Highly Significant)**
Grade III	8	503.3028	309.25844	201.30	1181.15	
Total	50	915.9412	659.15656	150.79	3530.00	

FIBROSCAN L.S AND PRESENCE OF VARICES

	N	Mean	Std. Deviation	Minimum	Maximum	P VALUE
Grade 0	6	21.283	2.3267	18.0	25.1	**<0.001** (Highly Significant)**
Grade I	21	33.867	8.1293	14.1	48.2	
Grade II	13	48.277	9.2487	23.8	57.2	
Grade III	8	71.213	5.6529	59.3	75.0	
Total	48	42.421	17.1934	14.1	75.0	

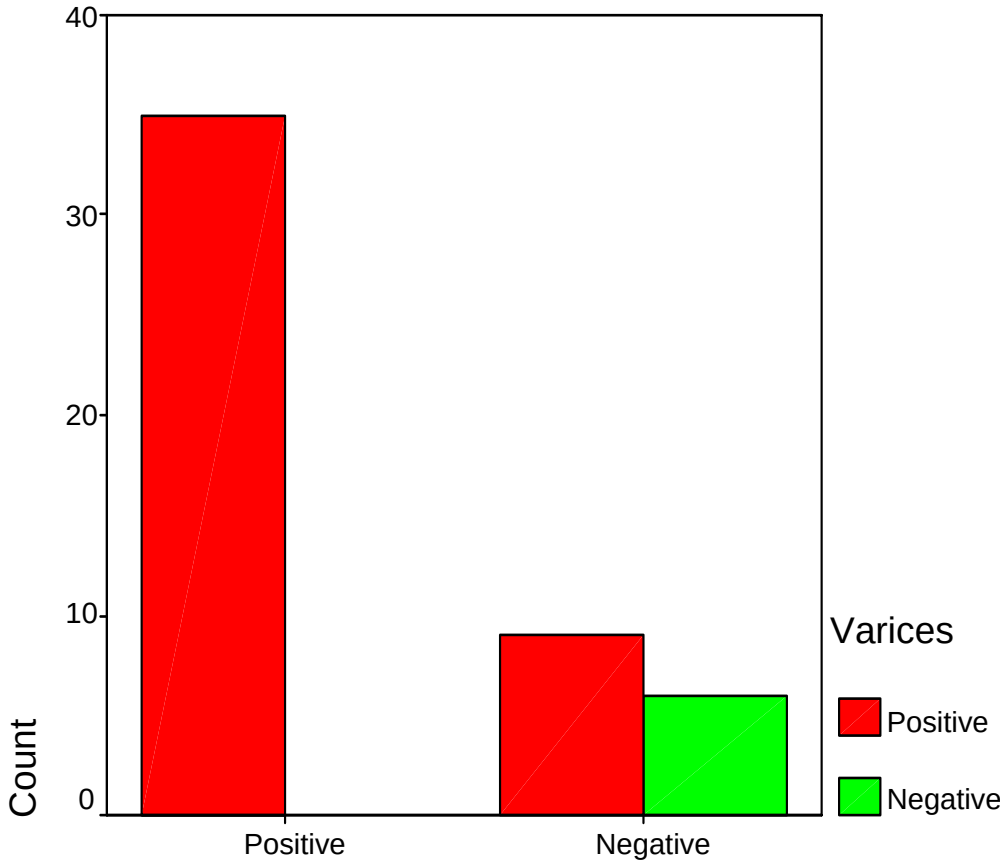
FIBROSCAN L.S AND VARIOUS GRADES OF VARICES

(I) Grade of Varices	(J) Grade of Varices	Mean Difference (I-J)	P.Value. Highly Significant
Grade 0	Grade I	-12.583(*)	.005
	Grade II	-26.994(*)	.000
	Grade III	-49.929(*)	.000
Grade I	Grade 0	12.583(*)	.005
	Grade II	-14.410(*)	.000
	Grade III	-37.346(*)	.000
Grade II	Grade 0	26.994(*)	.000
	Grade I	14.410(*)	.000
	Grade III	-22.936(*)	.000
Grade III	Grade 0	49.929(*)	.000
	Grade I	37.346(*)	.000
	Grade II	22.936(*)	.000

SENSITIVITY AND SPECIFICITY FOR FIBROSCAN L.S CUT OFF > 32kPa Versus * VARICES

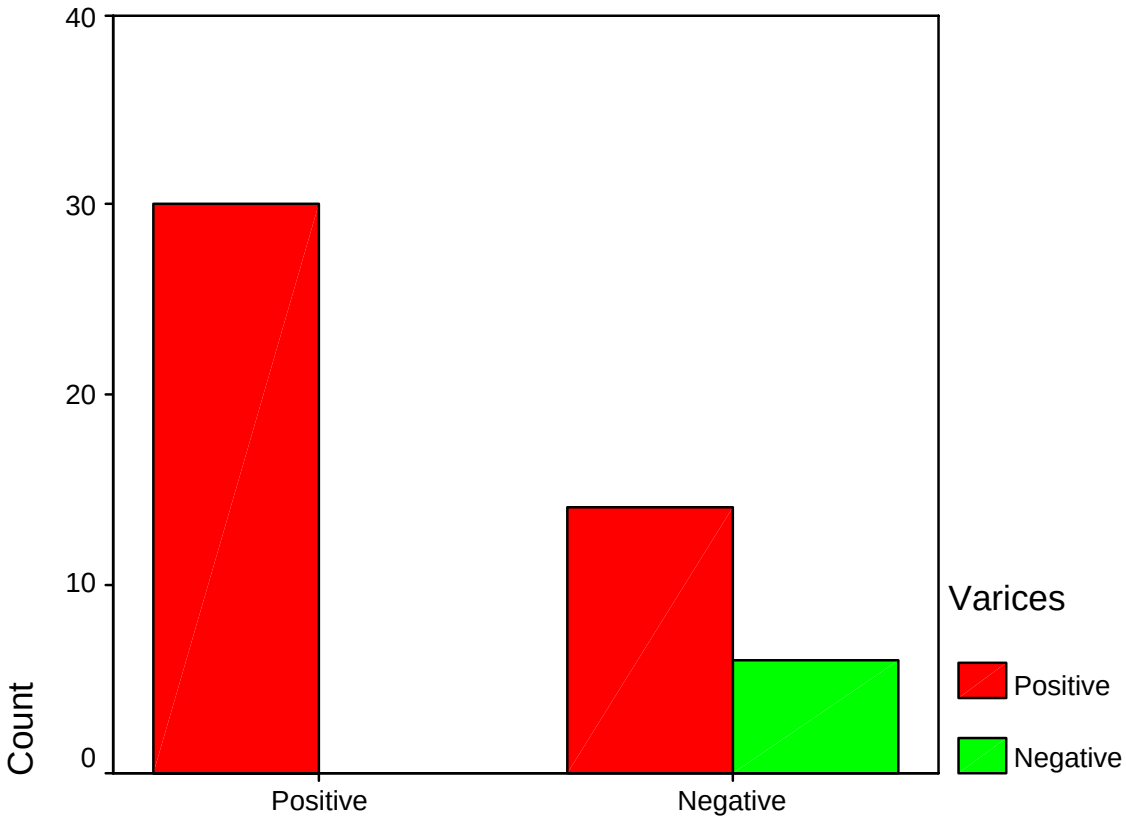
			Varices		Total	P Value
			Positive	Negative		
Fibroscan L.S > 32	Positive	Count	35	0	35	
		% within Fibroscan L.S > 32	100.0%	.0%	100.0%	
		% within Varices	79.5%	.0%	70.0%	
	Negative	Count	9	6	15	
		% within Fibroscan L.S > 32	60.0%	40.0%	100.0%	0.001
		% within Varices	20.5%	100.0%	30.0%	
Total		Count	44	6	50	
		% within Fibroscan L.S > 32	88.0%	12.0%	100.0%	
		% within Varices	100.0%	100.0%	100.0%	

SENSITIVITY AND SPECIFICITY FOR FIBROSCAN L.S CUT OFF > 32kPa Versus * VARICES



SENSITIVITY AND SPECIFICITY FOR PC/SD RATIO

			Varices		Total
			Positive	**Negative**	
PC/SD Ratio	Positive	Count	30	0	30
		% within PC/SD Ratio	100.0%	.0%	100.0%
		% within Varices	**68.2% Sensitivity**	.0%	60.0%
	Negative	Count	14	6	20
		% within PC/SD Ratio	70.0%	30.0%	100.0%
		% within Varices	31.8%	**100.0% Specificity**	40.0%
Total		Count	44	6	50
		% within PC/SD Ratio	88.0%	12.0%	100.0%
		% within Varices	100.0%	100.0%	100.0%

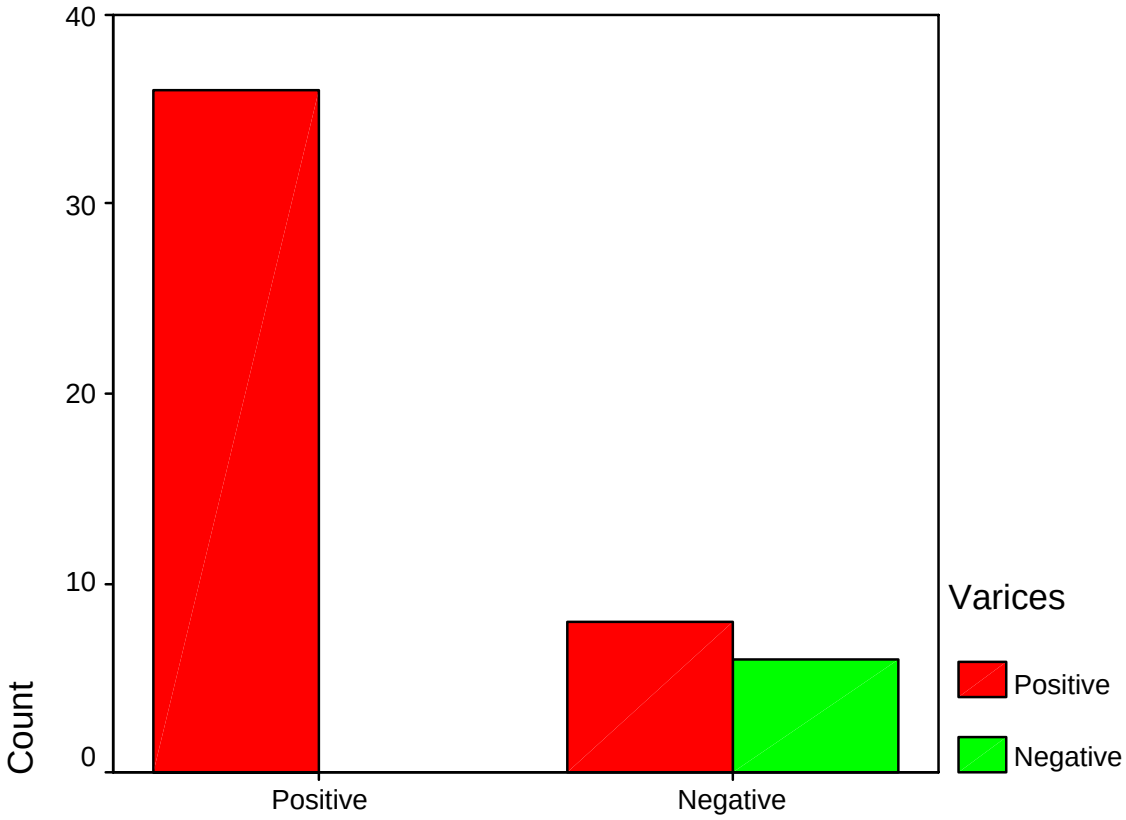


PC/SD Ratio < 909

SENSITIVITY AND SPECIFICITY FOR LS VALUE 29.7 kPa

			Varices		Total
			Positive	**Negative**	
Fibroscan L.S > 29.7	Positive	Count	36	0	36
		% within Fibroscan L.S > 29.7	100.0%	.0%	100.0%
		% within Varices	**81.8% Sensitivity**	.0%	72.0%
	Negative	Count	8	6	14
		% within Fibroscan L.S > 29.7	57.1%	42.9%	100.0%
		% within Varices	18.2%	**100.0% Specificity**	28.0%
Total		Count	44	6	50
		% within Fibroscan L.S > 29.7	88.0%	12.0%	100.0%
		% within Varices	100.0%	100.0%	100.0%

FOR A CUT OFF VALUE OF 29.7 kPa

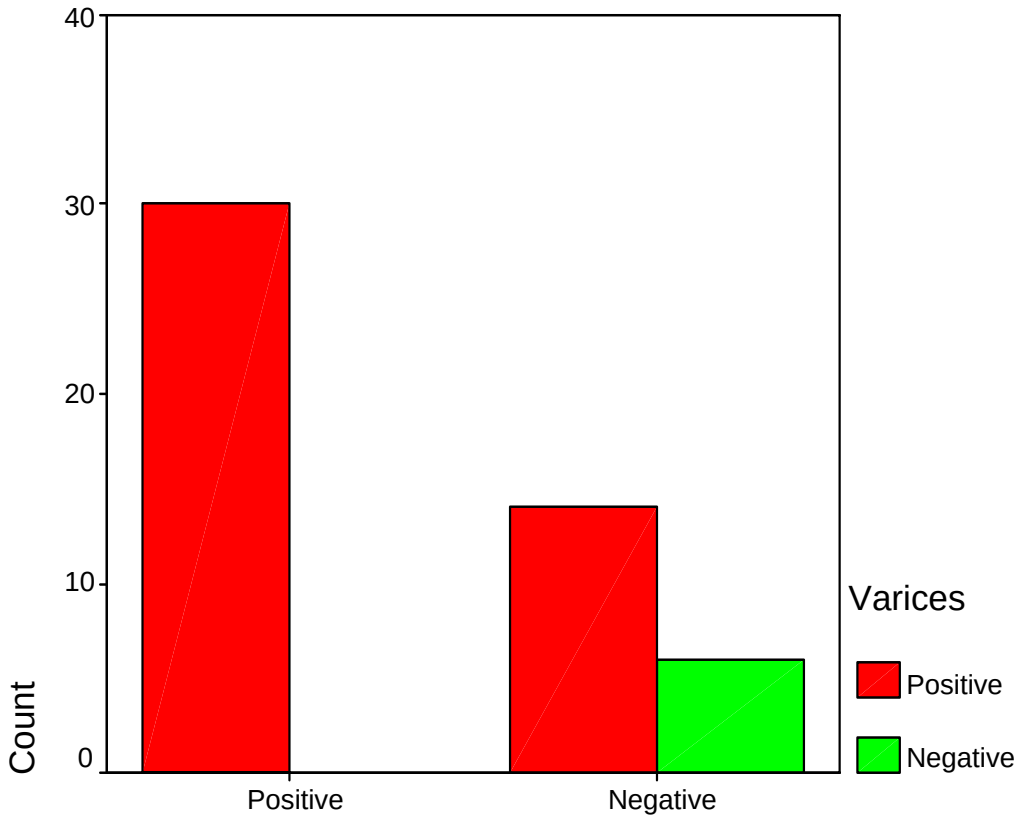


Fibroscan L.S > 29.7

PC/SD RATIO CUT OFF VALUE < 915.94 * VARICES

			Varices		Total	P Value
			Positive	**Negative**		
PC/SD Ratio < 915.94	Positive	Count	30	0	30	
		% within PC/SD Ratio < 915.94	100.0%	.0%	100.0%	0.002
		% within Varices	**68.2% Sensitivity**	.0%	60.0%	
	Negative	Count	14	6	20	
		% within PC/SD Ratio < 915.94	70.0%	30.0%	100.0%	
		% within Varices	31.8%	**100.0% Specificity**	40.0%	
Total		Count	44	6	50	
		% within PC/SD Ratio < 915.94	88.0%	12.0%	100.0%	
		% within Varices	100.0%	100.0%	100.0%	

PC/SD RATIO CUT OFF VALUE < 915.94 * VARICE



PC/SD Ratio < 915.94

DISCUSSION

Variceal bleeding is the most important complication of cirrhosis.

The first crucial step in prevention is the identification of patients who are at risk of bleeding by the use of OGD scopy , to subject them for prophylactic therapy. Since a variable proportion of patients will not have varices, screening of all patients with cirrhosis with upper GI endoscopy implies a number of unwanted OGD scopy which increase the work load of endoscopy units. In addition recommendations are limited on the compliance with endoscopic screening. Prediction of the presence of varices by non invasive modes would allow us to restrict the performance of endoscopy to those patients with ahigh probability of having the varices.

Our sample size consisted of fifty patients of whom 42 were male and 8 were female. Male constitute around 84% and female patients constitute about 16%.

Distribution of grades of varices was studied in various age group and no significant correlation was found.

No significant gender difference in the distribution of grade of varices was found.

Signs of liver cell failure was found in 48 of our patients constituting around 96% of the total.

Ascites was found in 9 of our patients constituting around 18% of the total.

Encephalopathy was present in 6 of our patients constituting about 12% of the total. Our study could not find any significant association between hepatic encephalopathy and varices.

Varices was positive in 44 of the patients constituting about 88% of the total and remaining 12% was found negative for varices.

Among the patients with presence of varices 23 had grade 1 varices constituting 46% of the total. 13 patients had grade 2 varices comprising 26% of the total. 8 patients had grade 3 varices comprising 16% of the total.

Child pugh scoring : 15 patients came under the category B and 35 patients came under category C. Relationship between non invasive parameters like serum bilirubin, serum albumin, hemoglobin, platelet count, spleen bipolar diameter to the presence of varices was studied. Among these only platelet count (P=0.001) and SD(P = 0.003) had statistical significance.

The results indicating the relevance of platelet count are on par with studies by thomplos et al (2003), madhotra et al (2002) , pilette et al (1999), shepis et al (1999), zaman et al(1999).

Studies by chalasani et al (1999), sanjay kumar et al (2006) , torres et al (1996) state that splenomegaly is an independent predictor of presence of varices.

PC/ SD RATIO INFERENCE

Patients were categorized in two groups based on cut off value of 909 for PC/SD ratio. Its relation to the grade of varices was studied. A significant difference between the presence or absence of varices and ratio of PC/SD of 909 was observed. (P =0.001) . This finding is in agreement with study by Gianni et al (2003). The use of platelet count / spleen diameter ratio overcomes the fallacy of using platelet count alone in predicting esophageal varices for the reason that platelet count may decrease in chronic liver disease due to several other factors. This ratio is introduced to take into consideration the decrease in platelet count which most likely depends on hypersplenism caused by portal hypertension.

Performing unwanted OGD scopy in all patients can be avoided if we take PC/SD ratio cut off 909, without running the risk of missing cases with esophageal varices.

Although thomopolos et al (2003) have put forth ascites as an independent predictor of presence of large varices, our study does not demonstrate a statistically significant correlation between presence and grade of varices and ascites.

FIBROSCAN INFERENCE

In our study all the patients were subjected to fibroscan and the correlation with the presence of esophageal varices was attempted.

We found that there was a statistically significant association between fibroscan value and the presence of varices represented by P = 0.001.

The mean fibroscan liver stiffness values are as follows

No varices - 21.28±2 kPa

Grade 1 varices - 33.867±8 kPa

Grade 2 varices - 48.27± 9 kPa

Grade 3 varices - 71.21±5 kPa

These values are on par with fibroscan study by Iulia et al (2008) . based on this study For a cut off value of 32 kPa the sensitivity and specificity was 79.5% and 100% respectively, which when compared to

study by Iulia et al where the values were found to be 58.44 and 72.22 % respectively.

For a cut off value of 62.8 kPa the sensitivity and specificity are 15.9% and 100% when compared to this reference study where the values of 24.6 % and 97.22 %. when a cut off value of 29.7kPa applied the sensitivity and specificity obtained are 81.8% and 100% respectively.

These values when compared on par with study by Mohamed said et al (2013) which were found as 95% and 77.3% for sensitivity and specificity.

For a cut off value of 42.42 kPa (mean fibroscan value)applied, the sensitivity is 50% and specificity is 100% Castera et al stated the optimal cut off vary from study to study, therefore optimal fibroscan cut off remains to be defined.

A study by Foucher et al, the cut off values for presence of grade 2/3 varices were 27.5kPa and 62.7 kPa respectively.

A study by Klibansky et al concluded that fibroscan as a more useful tool assessing clinical outcome like varices in cirrhotic patients.

In a study by Vizzuli et al a cut off value of 17 kPa was used for prediction of varices which when compared to our study and other studies it was found to be lower value cut off.

Kazemi et al concluded that fibroscan has the highest significant value followed by platelet count/ splenic diameter ratio for the detection of presence of varices.

SUMMARY AND CONCLUSION

SUMMARY

Fifty patients with newly diagnosed cirrhosis without prior history of bleeding were subjected to clinical evaluation. All patients underwent biochemical tests, such as liver function tests, complete hemogram , renal function tests, prothrombin time, ultrasonography of the abdomen to confirm the presence of cirrhosis and to record the spleen bipolar diameter, ascites and the presence of collaterals.

Fibroscan (transient elastography) was done to assess the liver stiffness values. Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them. We tried to identify non invasive parameters for prediction of esophageal varices in chronic liver disease patients. We assessed the role of platelet/ spleen diameter ratio and fibroscan for predicting esophageal varices in cirrhotic patients.

Presence of varices increase as patients progress to decompensated stage (child pugh score B & C) .

Decrease in platelet count was found to be an predictor of esophageal varices in patients with cirrhosis.

Ultrasound parameter spleen bipolar diameter also predicts the presence of esophageal varices.

When a cut off value of platelet count/ spleen diameter of ≤ 909 was employed in order to take into consideration the decrease in platelet count due to hypersplenism; it was found to be a good predictor of presence of esophageal varices.

The sensitivity of PC/SD ratio of ≤ 909 in predicting the presence of esophageal varices was 68.2% and for a ratio of 915.94(mean) it is found to be 62.8%.

Fibroscan measurement of liver stiffness value proves to be a significant prognostic tool for the prediction of esophageal varices.

A significant statistical association was observed between fibroscan values and the prediction of esophageal varices . (P = 0.001) For a cut off value of 32 kPa the sensitivity and specificity are 79.5% and 100% respectively.

For a cut off value of 62.8 the specificity was 100% and sensitivity was 15.9%.

CONCLUSION

Combining these two non invasive parameters , FIBROSCAN and ratio of PLATELET COUNT/ SPLEEN DIAMETER in patients with chronic liver disease can increase the reliability of predicting the presence of esophageal varices. Their use in screening and follow up of esophageal varices may substantially reduce the cost of health care and discomfort for patients as well reduce the burden of endoscopy units.

LIMITATIONS

1. Small sample size
2. Prospective studies were not done to validate the role of predictive parameters
3. Although we could show that combining the two non invasive parameters increased the percentage of varices being detected, the combined sensitivity could not be calculated.

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PROFORMA

Name :

Age:

Sex:

Occupation : Residence :

Clinical history: (including duration of CLD)

Pattern of consumption of alcohol:

Examination findings :

Basic investigation : CBC, LFT, RFT Viral markers:
HbsAg

Anti HCV

CBC		
RBC		
TC	DC N	L
	E	B
HB		
ESR		
PLATELET		
RFT		
Glucose		mg/dl
Urea		mg/dl
Creatinine		mg/dl
Na+		mEq/l
K+		mEq/l

LFT		
Total bilirubin		mg/dl
Direct bilirubin		mg/dl
SGOT		U/l
SGPT		U/l
ALP		U/l
Total protein		g/dl
Albumin		g/dl

USG abdomen :

Spleen size : ascites: yes/no

CXR

Fibro Scan in pKa Values

Endoscopy findings

Spleen platelet ratio

PATIENT CONSENT FORM

Study Title	:	"**PREDICTION OF ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS BY USING FIBROSCAN, SPLEEN SIZE AND PLATELET COUNT**"
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

☐

I hereby consent to participate in this study.

☐

I hereby give permission to undergo complete clinical examination, diagnostic tests including hematological, biochemical tests and radiological tests. ☐

Signature/ Thumb impression

Signature of the investigator

Patient's name and address

Study Investigator's name

Dr.M.PRASANNAKUMAR

INSTITUTIONAL ETHICS COMMITTEE

MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax: 044 25363970

CERTIFICATE OF APPROVAL

To

Dr.M.Prasanna Kumar,
Post Graduate,
Department of Internal Medicine,
Madras Medical College, Chennai - 600 003.

Dear **Dr.M.Prasanna Kumar,**

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Prediction of Esophageal Varices in Chronic Liver Disease Patients using Fibroscan, Spleen Size and Platelet Count"** No.50072014

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C.Rajendran, M.D,	-- Chairperson
2	Dr.R.Vimala, M.D, Dean, MMC, Ch-3	-- Dept Chairperson
3.	Prof. Kalaiselvi, M.D, Vice Principal, MMC, Ch-3	-- Member Secretary
4.	Prof. Nandhini, M.D, Inst. of Pharmacology, MMC, Ch-3	-- Member
5.	Prof.G.Muralidharan, M.S, Prof & HOD General Surgery, MMC, Ch-3	-- Member
6.	Prof. Md Ali, MD., DM., Prof& HOD of MGE, MMC, Ch- 3	-- Member
7.	Prof.Kala, MD., Director Inst. of O&G, Chennai-8	-- Member
8.	Prof.Ramadevi, Director I/c Biochemistry, MMC, Chennai	-- Member
9	Prof. Sasraswathy, MD., Director, Pathology, MMC, Ch- 3	-- Member
10.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
11.	Thiru.S.Ramesh Kumar, Administrative Officer, MMC, Ch-3.	-- Lay Person
12.	Thiru. S. Govindasamy, BA., BL	-- Lawyer
13.	Tmt.Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee